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F. Kh. Bakhteev (Bakhteyev)
Translated by James G. Dickson, *University of Wisconsin*

PARAMUTATION AND CHROMOSOME ORGANIZATION

R. A. Brink, *University of Wisconsin*

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THE MELANOCYTES OF MAMMALS

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ABSTRACT

Melanocytes may be regarded as unicellular, pigment-secreting glands, largely though not entirely confined to the epidermis, of which they are a constant though often unrecognized cellular component. Their numerical incidence, and their branching form, with numerous dichotomizing processes, are such as to form a reticular system within the epidermis. Evidence is evaluated that they are a race or lineage of cells sui generi; and form a self-maintaining system within the epidermis. Their product—melanin granules—is secreted directly into the cytoplasm of neighboring Malpighian cells upon which the processes of the melanocytes terminate in the form of small swellings or end-caps. The several types of branched cells demonstrable within the epidermis by various techniques are discussed in relation to their identity as living melanocytes, or as effete cells of this lineage which, having lost or discharged their pigment, participate in the general outward movement of epidermal cells to be lost from the skin surface.

The color variants of skin and hair, including spotting and albinism, are the direct result of melanocyte activity, and have been shown to be determined by the action and interaction of multiple genes, some of which operate via the milieu in which the pigment cells reside and others of which appear to act intracellularly and to control the biochemical steps of melanogenesis.

The problem of pigment spread is discussed and related to the anatomy of the melanocyte system and to the co-existence of variant types of melanocytes within a single individual.

I. INTRODUCTION

FOR NEARLY a century the existence, origin, and functional significance of branched cells, variously described as melanoblasts, melanophores, dendritic cells, melanogenocytes, melanodendrocytes, stellate cells, chromatophores, "cellules amboceptrices," cells of Langerhans, and melanocytes, in the epidermis of mammalian skin has been controversial. (The term "melanocyte" has now been adopted by unanimous agreement—see Gordon, 1953). This state of discord stemmed mainly from the fact that even the small minority of investigators who succeeded in demonstrating these cells (including Langerhans, 1868; Riehl, 1884; Aeby, 1885; Ehrmann, 1885; Kölliker, 1887; Becker, 1927; Bloch, 1916, 1929) could usually only do so rather sporadically, and the others were naturally unwilling to accept the existence of what they had been unable to see for themselves. Only within the last two decades have reliable and reproducible techniques been introduced whereby these cells could be revealed at will, even in the *living* condition, isolated from neighboring Malpighian cells, transplanted, cultured in vitro, and almost selectively destroyed in intact skin, so that their origin, incidence, exclusive role in integumentary pigmen-

tation, and general biology could be elucidated. These cells, which are present in all vertebrates —they have even been observed in the skin of a fossil ichthyosaur more than 150 million years old (Whitear, 1956)—are almost unique among vertebrate cell types in respect to the number of disciplines that include them in their curricula. At least four international conferences (see Miner, 1948; Gordon, 1950, 1953, 1959) have been specifically devoted to pigment cells since 1948, further evidence on the interest centered upon them. No other cell of the body except possibly the erythrocyte has attained such an exalted status.

The purpose of this review is to give a general account of these branched cells as they occur in the epidermis and to a lesser extent in other tissues of mammals, though mention will be made of the extensive studies conducted on their homologues in other vertebrates, particularly birds, when pertinent to an understanding of the biology of the mammalian pigment cell. No apology need be rendered for including a fairly detailed account of the anatomy of the mammalian epidermis, since it constitutes the environment within which most melanocytes are found and of which they are a constant *structural* ingredient.

II. THE REGIONAL AND COMPARATIVE ANATOMY OF THE EPIDERMIS

The statement that the epidermis is a stratified, squamous epithelium which invests the outer surface of the mammalian body without interruption is highly uninformative about its fine structure, its regional variation in the body, or its variation from species to species. Indeed its functional and morphological versatility surpasses that of all other tissues.

Only in the cornea and in scar tissue is the epidermis of constant thickness, with a plane surface of contact or union with the underlying dermis or corium. Elsewhere, the inner surface of the epidermal epithelium is corrugated, being distorted into a pattern of "hills and valleys" which is exactly complementary in structure to the upper or papillary layer of the dermis. The dermal papillae, as seen in orthodox transverse sections of skin, are in fact very rarely papillae, but transverse sections of elongated ridges which alternate with downward projections of the epidermis (sometimes referred to as rete pegs) which are also elongated epidermal thickenings (see Fig. 1). The anatomy of the epidermis is best studied by removing it in its entirety from the dermis, fixing and staining it as required—the use of pigmented skin may obviate the need for any stain at all—and examining it from its inner side (Fig. 2). Complete separation may be effected in a variety of ways: enzymically, by digestion of thin skin shavings in crude trypsin solutions (Medawar, 1941; Billingham and Medawar, 1948a; Szabó, 1955); by heating skin to 50° C.; by treating it with weak ammonia solution (Baumberger, Suntzeff and Cowdry, 1942) or with weak

FIG. 1. CONVENTIONAL TRANSVERSE SECTION OF PIGMENTED SKIN FROM PIG'S SNOUT SHOWING A TYPICAL HIGHLY CONVOLUTED DERMO-EPIDERMAL INTERFACE

Downward projections of the epidermis (sometimes referred to as *rete pegs*) alternate with upward projections of the dermis known as dermal papillae. That this section gives a highly misleading impression of the true nature of the spatial relationships between dermis and epidermis is indicated by figure 2, photographed at the same magnification. × 40.

FIG. 2. SHEET OF UNSTAINED SUPERFICIAL EPIDERMIS ENZYMICALLY DETACHED FROM THE SKIN OF A PIG'S SNOUT AND VIEWED FROM THE UNDERSIDE

The specimen is unstained since the melanin granules depict the cellular outlines. The "hill and valley" contour pattern is highly developed and orientated about the hair follicles. The ridges or hills are the "rete pegs" as seen in transverse sections, whereas the valleys are the spaces formerly occupied by the dermal papillae. × 40

FIG. 3. SUPERFICIAL EPIDERMIS FROM SKIN OF THE EAR OF A BLACK GUINEA PIG IN WHICH THE MELANOCYTES HAVE BEEN "INTENSIFIED" BY THE DOPA METHOD. × 400

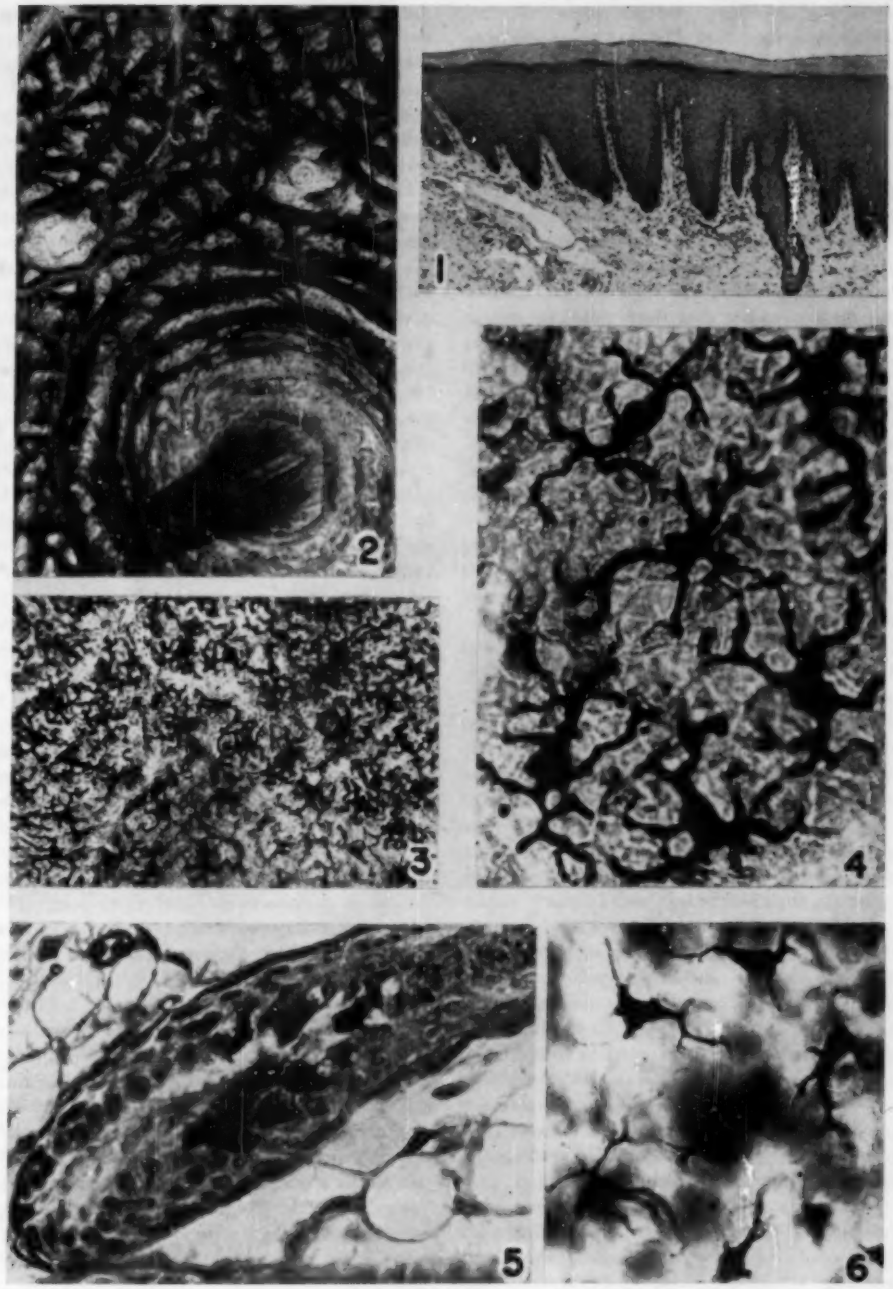
FIG. 4. MELANOCYTES FROM PIGMENTED TRUNK SKIN EPIDERMIS OF THE GUINEA PIG "STAINED" BY THE DOPA METHOD

Note the abundant branches at the ends of some of which the terminal dilations or end-caps can be seeen. The Malpighian cell outlines can just be discerned. × 900

FIG. 5. UNSTAINED SAGITTAL SECTION THROUGH THE BULB OF A PIGMENTED MOUSE HAIR FOLLICLE TO SHOW THE MELANOCYTES. × 700

FIG. 6. BRANCHED CELLS REVEALED IN HIGHER LEVELS OF THE EPIDERMIS OF CAUCASIAN SKIN BY A GOLD-IMPREGNATION TECHNIQUE

These are the so-called cells of Langerhans which are held to represent the perikarya of effete melanocytes. × 700



FIGS. 1–6.

acetic acid solutions (Felsher, 1946; Cowdry, 1950; Fleischauer, 1952; Horstmann, 1952); or by treating skin with 2*N* sodium bromide (Staricco and Pinkus, 1957). Of these methods the enzymic one has the distinctive advantage that it leaves the cells alive so that sheets of epidermis so prepared can be grafted (Billingham and Reynolds, 1952), stained supravitally (Billingham and Medawar, 1953) or used for enzymic studies.

The "hill and valley" pattern presented by the undersides of these pure epidermal preparations is regular, repetitive, and to a considerable extent distinctive for skin from different regions of the body (see Fig. 2). The thicker the epithelium, the bolder is this relief. In the general body skin epidermis of hair-bearing mammals, which is usually very thin and comprises little more than the Malpighian or basal layer overlain by a thin cuticle, the hills are very low and flattened, the valleys being correspondingly broad and shallow. In guinea-pigs and mice it has been shown that the orientation of this broad "hill and valley" pattern of the trunk epidermis is related to that of the more or less dorso-ventrally oriented rows or clusters of hair follicles. The hills are elongated epithelial thickenings about half as thick again as the valleys, running at right angles to the direction of hair slope and abutting against the obtuse angle of the emergent hairs. Occasionally they may fuse with their neighbors or bifurcate at an acute angle to give a Y-shaped junction. The valleys lie in the acute angle of the emergent hairs. Where the hair density is low or zero, as on the ears, tails, gonads, or soles of the feet in most fur-bearing mammals, the epidermis is usually much thicker and tends towards the complete multi-layered stratigraphic pattern so characteristic of human skin, and the hill and valley pattern is more highly developed. For example, guinea-pig ear skin epidermis is very similar to human facial skin and the skin of the sole of its foot is strikingly similar to that of man. In the guinea pig's sole, for once, the dermal papillae are rounded upward projections so that viewed from its underside, the separated epidermis resembles an incompletely perforated plate.

In man, the epidermis of the abdomen and of the anterior surfaces of the forearms and tibia has its simplest pattern, with very shallow and infrequent hills. In the scalp, the dermo-epidermal interface is fairly flat except near the necks of the follicles and glands about which local ridging systems are oriented. However bold the hill and valley pattern of the epidermis may be, only very rarely is it reflected by the presence of elevations and depressions at the skin surface—e.g., the so-called friction ridges on the palmar and plantar surfaces of man.

Illustrated accounts of the anatomy of human epidermis in various regions of the body have been presented by Blaschko, 1887; Emslie and Weinman, 1949; Cowdry, 1950; Fleischauer, 1952; Horstman, 1952; and Szabó, 1959. The epidermal anatomy of other mammals has been less extensively studied (see Billingham and Medawar, 1948a, 1953; Medawar, 1953; Reynolds, 1954). Since the thickness of the epidermis normally remains constant it is evident that the loss of its cells by desquamation from the surface is constantly balanced by the generation of new cells. The evidence is almost unequivocal that the Malpighian system is reproductively self-maintaining through the activity of generative cells located in the basal layer and receives no reinforcement through the transformation of immigrant mesenchymal cells, as some workers have claimed (Andrew and Andrew, 1949, 1954). In rabbits, a multilayered epithelium is regenerated anew within a week or two from a suspension of living epidermal cells prepared from sheets of enzymically separated ear skin epidermis and "seeded" over an extensive raw area from which the *entire thickness* of the skin, including even the deepest follicle rudiments, has been removed. However, if epidermal cells are not transplanted to such areas, new epithelium does not reappear on them spontaneously, and resurfacing takes place only as a consequence of inward migration of epithelium from the wound margins (Billingham and Reynolds, 1952).

Claims that, contrary to the usually held view, mitosis is not the sole prerogative of the basal layer (Thuringer, 1924, 1928; Cowdry and Thompson, 1944) do not withstand critical analysis. As Medawar (1953) points out, it is highly improbable that the known exacting metabolic requirements for the initiation of mitosis can be met in the vascular quarantine of the prickle cell layer. The most likely explanation of the presence of mitotic figures in this layer is that they represent cells that *began* their division in the basal layer. It is almost inconceivable that prickle cells are capable of division, since they probably

have already passed irrevocably along the pathway to keratinization. Furthermore, as Billingham and Medawar (1953) have pointed out, the mitoses seen in what *appear* to be relatively superficial strata in vertical sections of a thick epidermis may really be juxtaposed to the dermal papillae. This follows since in certain patches the plane of the section will be tangential to the walls of the steeply rising papillae, in which case the section, though vertical in the usual sense, will be anatomically horizontal, since it runs in the plane of the dermal-epidermal interface.

Although various estimates have been made of the renewal time of the epidermis (see Pinkus, 1954), the most accurate is probably that of Storey and Leblond (1951) who, using an autoradiographical labelling technique, obtained a value of 19.1 days for the renewal time of the plantar epidermis of adult rats at a temperature of 27° C. So far as we are aware, no one has ever investigated whether the incidence of mitoses in the epidermis is always higher on the hill regions than in the valleys, though examination of many illustrations (see Storey and Leblond, 1951) suggests that it is probably so. Billingham and Medawar (1953) found that mitoses were 10–15 times more frequent in the hills of trunk skin epidermis of the guinea pig than in the valleys and they suggested on this and other evidence that the epidermal cell population in the valley regions is maintained by the division of cells elsewhere—presumably in the hill regions where the epidermis is thicker and mitoses more abundant. In a thick epidermis, such as that of the sole of the foot, where the hills and valleys are highly developed, the current of displacement of epidermal cells must be predominantly outwards rather than both sideways and outwards as in the case of trunk skin epidermis of guinea pigs.

Different Types of Epidermis

The types of epidermis covering certain regions of the body not only differ with respect to thickness and the patterns of hill and valley systems, but also vary profoundly and abruptly in outward appearance and in histological and cytological properties. For example, the sole of the foot has a thick and mitotically active epidermis, bounded by a compact multilayered cuticle. The epithelium of the cornea is exquisitely transparent, probably because of the thin, non-flaking nature of its cuticle and distinctive properties of its cells. Similar combinations of highly distinctive characters underlie the biological uniqueness of other epidermal epithelia, including those of the tongue, the germinal matrix of the nails and claws, and the vagina. That these various qualitative differences are innate, and are not merely due to local peculiarities of the positions occupied by the epithelia, have been shown by experiments in which epithelia have been transplanted to anatomically unnatural positions (Billingham and Medawar, 1948b, 1950a; Krohn, 1955). For example, if thin shavings are removed from a rabbit's cornea and placed at the center of a large raw area prepared in the skin of the side of its chest, the epithelial cells proliferate and migrate outwards from the graft margins as an intact sheet of epithelium several layers in thickness. Despite the fact that it is growing over an intensely vascular bed (provided by granulation tissue), and may increase its area up to fifty-fold, this epithelium rigidly conserves its transparency and other distinctive properties. A similar story can be told of the epithelium of thin ear skin grafts transplanted to shallow horizontal pockets cut in the corneas of rabbit's eyes (Billingham and Medawar, 1950a). The skin epithelium retains its specificity in this avascular environment. One more striking example: if skin from the sole of a guinea pig's foot is transplanted to its chest, despite its protection by the hair and almost complete exemption from the wear and tear of every day life, it continues to manufacture layer upon layer of now functionless cuticle with unabated activity for the rest of the animal's life. As Billingham and Medawar (1948a, 1948b, 1950a) have argued, these different types of Malpighian systems are not functional adaptations, but are of developmental origin, and are perpetuated in somatic cellular heredity. The term "epidermis," like "fibroblast," refers to a *genus* comprising several distinct cellular species.

So far this section has dealt exclusively with the superficial epidermis and its variants. However, in nearly all mammals by far the greater portion of the epidermis lies concealed from view, imbedded in the dermis, where it constitutes the hair follicles and their associated glands. The structure and cyclical activity of these appendages have been well described and reviewed elsewhere (Chase, 1954a; Montagna, 1956; Montagna and Van Scott, 1958), and require no fur-

ther elaboration here. The only epidermal portions of a follicle that are normally permanent are the sebaceous glands and their ducts and the apical part, or neck, of the follicle between the openings of these ducts and the skin surface. Despite their much greater structural complexity, it seems that neither the whole nor any portion of the follicles can be regarded as a true-breeding species or lineage of cells of the Malpighian system. This follows since (a) after the complete excision of the superficial epidermis, even down to a level which leaves behind only follicle bases, the superficial epidermis will be regenerated anew through the proliferative and migratory activity of cells in the follicle remnants (Billingham and Medawar, 1950b; Pepper, 1954), and (b) follicles can be regenerated de novo from the superficial epidermis in certain adult mammals, either under experimental conditions (see Breedis, 1954; Billingham and Russell, 1956) or naturally during regeneration of the "velvet" of deer antlers (Billingham, 1958; Billingham, Mangold, and Silvers, 1959).

III. THE REVELATION OF MELANOCYTES

Nothing has contributed more to the great delay in recognizing melanocytes as *constant* ingredients of mammalian epidermis than the lack of reliable methods for revealing them consistently in skins of different colors. That melanin, the granular pigment of the skin, originates *within* the epidermis has long been agreed; and that melanogenesis is associated with the presence of branched cells within the epidermis was inferred by many workers from a variety of observations. For example, branched cells were more or less specifically defined by methods which bring about the reduction of gold or silver upon the fine melanin granules; they *appear* to be more numerous and to have more prominent and more complex branches in Caucasian skin which has been irradiated and therefore is the site of active pigment formation; and it has long been known that they are associated with pigment patterns in lower vertebrates.

Despite its name, melanin is not always black; its granules range from black and dark sepia to light yellow. The paler its color, the smaller and less conspicuous are its granules (Russell, 1949a), so that in very pale skin their presence can only be revealed by treatment of sections with some reagent that blackens them. Bizzozero (1908) employed silver nitrate solution for this purpose, but subsequently Masson (1926, 1948a) showed that more sensitive and consistent results could be obtained by substituting ammonium silver nitrate solution. He claims that under definable conditions this method, applicable to both paraffin sections of fixed tissues and to frozen sections, is completely specific for melanin. By means of these silver techniques, systematic investigations in man have shown that melanin is present throughout the epidermis of the integument and in the epithelium of the mucous membranes, including that of the buccal cavity and the pharynx.

Within the epidermis pigment is most abundant at the level of the basal layer, being present in progressively decreasing amounts in the more superficial strata. In deeply pigmented skin where melanin is abundant, as in that of the Negro or black guinea pig, it is distributed diffusely throughout the cytoplasm of the Malpighian cells, but in less heavily pigmented skin it tends to be more concentrated in the upper region of the Malphigian cells, occupying the characteristic "nuclear-capping" position which many workers regard as a protective screen against irradiation. Although it has sometimes been questioned whether melanin is actually present *within* the cytoplasm of Malphigian cells, Billingham's (1948) studies on living dissociated cells prepared from the enzymically detached epidermis of pigmented guinea pig's skin left little doubt that this is where the pigment is located, an inference subsequently confirmed by electron microscope studies on the superficial epidermis and on the epidermis of the matrix of hair follicles (Laden, Linden, and Erickson, 1953; Birbeck, Mercer, and Barnicot, 1956).

In orthodoxly stained transverse sections of pigmented skin, branched melanocytes may occasionally be observed and as such have been repeatedly figured in the older literature (Riel, 1884; Aeby, 1885; Kölliker, 1887; Ehrmann, 1885). Unfortunately, without resort to special techniques, ability to distinguish them in transverse paraffin sections is highly unpredictable and depends upon the level of pigmentation of the skin; they are rarely recognizable in either very heavily pigmented or in very lightly pigmented skin. However, the ammonium silver nitrate technique may outline melanocytes in sections of feebly pigmented skin with striking clarity; not because of any specific staining of the cyto-

plasm, but simply because of the darkening of the fine pigment granules within it. Because of the masking effect of the abundant pigment, this silver impregnation technique reveals very few melanocytes in a heavily pigmented epidermis, though the bodies or perikarya of the melanocytes may be recognized in very thin sections (Masson, 1948a) because they are often *less* pigmented than the surrounding Malpighian cells.

One of the most important events in the study of the anatomical basis of epidermal pigmentation was the introduction of Dopa (3,4-dihydroxyphenylalanine) by Bruno Bloch (1916, 1929) as a "stain" for cells capable of elaborating melanin. By analogy with oxidase-type enzyme systems in both plants and lower animals, which are capable of producing melanic substances from polyphenols (chromogens), Bloch assumed that a similar enzyme system was responsible for epidermal melanogenesis. In his search for the chromogen, or pigment precursor, in mammals he followed up as a clue the hyperpigmentation of the skin which accompanied a certain type of lesion of the adrenal (Addison's disease), and experimented with the cyclic amino acid most closely related to adrenalin—Dopa. Incubation of frozen sections of fresh skin in weak aqueous solutions of this substance, buffered to *p*H 7.4, in the presence of air, resulted in the selective darkening of the entire cytoplasm of certain cells due to the formation of intensely black Dopa melanin. Bloch strongly maintained that Dopa is the normal chromogen and that it is transformed into melanin by a specific intracellular enzyme, Dopa oxidase. From this reasoning it followed that any cell which was Dopa-positive, i.e., could bring about the blackening of this reagent within its cytoplasm, must be a pigment-producing cell.

Bloch found that a great enhancement of the Dopa reaction in the epidermis followed a melanogenic stimulus such as irradiation, the number of melanocytes demonstrable being greatly increased. Even without the aid of the Dopa reaction, previous workers had noted that branched cells seem to *appear* in the epidermis as a consequence of irradiation (see Meirowsky, 1940). Thus the idea gradually gained ground that these branched cells were responsible for pigment formation. Bloch's not infrequent failure to fix his fresh tissues *before* carrying out the Dopa reaction misled him into believing that the ordinary, rounded, and unbranched Malpighian cells were also capable of forming pigment, since they sometimes gave a positive reaction. Subsequently, other workers demonstrated that when formol-fixed tissues were treated with the Dopa reagent, the Malpighian cells were never Dopa positive. Various refinements in technique, by Becker, Praver and Thatcher (1935) and Laidlaw and Blackberg (1932), have freed the Dopa reaction from capriciousness and made it an exceedingly simple and invaluable tool for pigment cell research.

Soon after its introduction the specificity of the Dopa reaction for pigment-producing cells was severely criticized on the grounds that such varied cells as leucocytes, mast cells, and erythrocytes, which never produced melanin, were Dopa positive, presumably since they contain nonspecific polyphenol oxidases. However, all workers are agreed that so far as the epidermis is concerned the Dopa reaction affords a perfectly valid means of selectively revealing those cells which possess an active melanogenic system (Russell, 1939; Ginsburg, 1944).

Since melanocytes are branched cells whose processes travel out horizontally and vertically many cell diameters away, transverse sections, although essential for studying the stratigraphic position of melanocytes in the epidermis, are highly unfavorable for studying the incidence and pattern of distribution. The ideal material comprises sheets of enzymically separated epidermis, which can be examined from the lower side. In the epidermis isolated from pigmented guinea pigs' skin no staining procedure whatsoever is required to reveal the melanocytes and their system of dichotomizing branches in their entirety, as their own complement of pigment granules does this quite adequately. Yet, such cells may be almost undetectable in transverse sections of similar skin. Certainly with these pure epidermal preparations of deeply pigmented guinea pig skin, "staining" with Dopa makes the melanocytes stand out more boldly, but adds little to what can be seen in the unstained material (Figs. 3 and 4). To show melanocytes in human skin, however, whether of Caucasian, Indian or Negro type, the use of the Dopa reaction is almost obligatory. In Caucasian skin there is too little pigment to reveal the melanocytes, unless the pigment is intensified by the silver technique or the cytoplasm of the melanocytes darkened by exposure to Dopa; whereas in the

skin of the deeply pigmented races, the abundant golden-yellow, semitranslucent pigment granules seem to obscure the melanocytes unless the cytoplasm is darkened with Dopa melanin.

One other method of revealing the melanocytes in lightly pigmented or even in apparently non-pigmented Caucasian skin involves immersion of viable epidermal sheets in a weakly alkaline physiological solution containing a low concentration of a quinone-imine dye (Conn, 1946) such as methylene blue, toluidine blue, or brilliant cresyl blue. The cytoplasm of the perikarya and branches of the melanocytes become bright blue as a consequence of their ability to maintain these redox dyes in the oxidized state (Billingham, 1948; Billingham and Medawar, 1953). The fact that the perikarya and processes of melanocytes, at first blue on account of the supra-vital staining, blacken on subsequent treatment with Dopa leaves no doubt that Dopa-positive and quinone-imine dye positive cells of the basal layer of the epidermis are melanocytes.

IV. THE MELANOCYTE SYSTEM OF THE SUPERFICIAL EPIDERMIS

A detailed account of what each of the various techniques described has revealed of the melanocyte population of the epidermis, or of the particular findings of different investigators would be exceedingly tedious because of the high degree of overlap of opinion which has been attained during the last decade. The following account is a synthesis of the abundant information available.

Melanocytes are *constant* cellular ingredients of the superficial epidermis of mammals, lying regularly distributed among the basal layer cells of the Malpighian system. Each melanocyte consists of a perikaryon slightly larger than a Malpighian cell. It is always located at the dermo-epidermal interface and not infrequently abuts slightly into the dermis just below this general level. This perikaryon in most instances is slightly elongated horizontally, and gives rise to a variable number of primary branches, usually 4 or 5. The branches diverge, repeatedly subdividing and becoming attenuated as they weave horizontally and upwards between the Malpighian cells that separate them, and may extend as far as 100μ from the parent cell body (Figs. 3 and 4). Each branch ends in a sort of swelling or button which is strongly Dopa positive, intimately applied to the terminal pole of a Malpighian cell. The distribution of melanocytes and their mode of branching is normally such that scarcely a basal layer Malpighian cell is without contact with one of their end-caps, since the territories of individual melanocytes are contiguous. Careful study of pure epidermal preparations has shown that in some instances a branch of a melanocyte may terminate not on a Malpighian cell but on the cell body of a neighboring melanocyte. Confluence of processes between melanocytes is less frequently observed, and probably represents the end stage of cell division (Billingham and Medawar, 1948a).

Melanocytes are most densely concentrated at the summits and sides of the epidermal ridges or hills in skin regions where the dermo-epidermal interface presents a highly convoluted pattern. In the epidermis of the skin of the guinea pig's trunk, living melanocytes are completely absent from the valley regions and are, therefore, absent from an area comprising between one-third and two-thirds of the skin surface. Moreover, as will be shown in a following section, the melanocytes in the hills of trunk skin epidermis are spaced further apart than in the much thicker and more highly convoluted ear skin epidermis.

Apart from enormous variation in the individual branching patterns of melanocytes, the shapes of their perikarya vary greatly. They may be fully dendritic cells, giving off several branches in many directions, or they may be fusiform or fibroblast like, with only two terminal processes. Szabó's (1954) extensive studies on human melanocytes led him to conclude that, although the shapes of these cells are probably largely influenced by mechanical factors prevailing in the milieu in which they are found, there is apparently a clear-cut dimorphism, particularly in the skin of the cheek and forehead where large melanocytes with abundant cytoplasm are found among more numerous smaller melanocytes. Further evidence concerning the morphological variations of these cells will be presented in section XI.

In colored rabbits, rats and mice the very thin superficial epidermis of the trunk is either unpigmented or its cells contain almost undetectable amounts of melanin. Here, although melanocytes are present, sparsely scattered over the broad hill regions, they are normally Dopa negative, presumably because their melanogenic fac-

ulty has never been properly awakened. However, they can be made to produce pigment and react with Dopa following treatment of the skin with irritants (Burgoyne, Heston, Hartwell, and Stewart, 1949; Reynolds, 1954; Silvers, 1958d).

As long ago as 1926, Masson designated as "cellules claires," or clear cells, certain fairly numerous and conspicuous cells in the basal layer of transverse sections of Caucasian skin stained by the trichrome method. His identification of these cells as the perikarya of melanocytes, based largely on their staining properties with Dopa and with ammonium silver nitrate, has been fully endorsed by subsequent studies (Masson, 1948a, b; Billingham, 1948; Zimmermann and Cornbleet, 1948; Billingham and Medawar, 1953).

Clear cells differ from the neighboring Malpighian cells by the non-basophilic nature of their cytoplasm, which is almost transparent, and by the staining properties and structure of their nuclei which have large nucleoli. Unlike Malpighian cells it is exceedingly difficult to fix the clear cells; their cytoplasm usually appears to be retracted around the nucleus, leaving a vacuole-like space formerly occupied by the extended protoplasm. These cells never have tonofibrils and are not united to neighboring cells by "prickles," whatever the nature of these bridge-like structures may be (see Medawar, 1953). From the bodies of these cells, protoplasmic branches are given off which can usually be followed outwards for a short distance.

Although clear cells can rarely be seen in vertical sections of heavily pigmented skins because of the abundant pigment granules occupying their cytoplasm, they stand out boldly if the pigment granules are removed by a bleaching procedure before the sections are stained (Billingham and Medawar, 1953). A recent study of the clear cells of human epidermis with the electron microscope has confirmed previous interpretations concerning the structure and nature of this cell (Clark and Hibbs, 1958).

The ubiquity of melanocytes in the superficial epidermis is very nearly complete. In man, the pioneer survey of Becker (1927) has been augmented by more recent studies, particularly those of Szabó (1954, 1959). Melanocytes have been found in all regions of the cutaneous surface, in the nasal epithelium and in that of the pharynx where, contrary to expectation, some pigmentation normally occurs. Melanocytes have not been reported in the human esophagus and mammary gland though pigment accompanies the lacteal ducts for a short distance in the nipple (Becker, 1927). In the pig, melanocytes evidently are not infrequently present in the ducts of the mammary glands, where the pigment they elaborate is responsible for an unsightly appearance of bacon (Cole, Park, and Deakin, 1933).

Not quite all epidermal epithelia are equipped with melanocytes. They are absent not only from the necks of hair follicles around the level at which the sebaceous glands open, but also from the cornea and, at least in the guinea pig, from the tongue (Billingham and Medawar, 1948a, 1953).

It is of some importance, as will be seen later (Section XII), that the presence of melanocytes in the basal layer of the superficial epidermis of the white ears and broad, shallow hill regions of the trunk skin of recessively spotted guinea pigs (Billingham and Medawar, 1953) or mice (Reynolds, 1954) cannot be revealed by any of the techniques described in the previous section.

V. NUMERICAL INCIDENCE OF MELANOCYTES IN THE EPIDERMIS AND RELATION TO SKIN COLOR

Once the considerable advantages of whole mount preparations of the separated superficial epidermis, or even of thin superficial shavings of skin (Billingham and Medawar, 1953), pretreated with the Dopa reagent to make the melanocytes stand out more boldly, were appreciated, strictly quantitative studies on melanocytes became a practical possibility. Accurate counts of the number of these cells per mm^2 of dermo-epidermal interface in plane projection could easily be made. In addition to objective studies on the relationship of melanocyte density to pigmentary activity, investigations have now been made of the variations in melanocyte density in relation to the regional anatomy of the epidermis and in relation to pathological abnormalities of the skin in man.

Billingham and Medawar's (1948a, 1953) studies of the pigmented skin of parti-colored (particularly red and black) guinea pigs showed that the melanocytes, like Malpighian cells, may exist in a single individual in a variety of "true-breeding" cellular "species," i.e., variant forms which preserve their distinctive characters even after transplantation to anatomically and physiologi-

cally foreign environments. For example, "black" and "red" melanocytes may form conspicuously distinct species in a single guinea pig. Differences between red and black pigmentation in the same animal might be attributed to characteristic differences between the densities of melanocytes—for example, red skin might have fewer melanocytes per unit area than black skin—but this explanation has been shown to be incorrect. Thorough numerical studies on the cellular composition of red and black guinea pigs' skin have failed to reveal any significant difference in structure, number or distribution between the melanocytes of symmetrically opposite areas of different color (Billingham and Medawar, 1953). Although there are considerable variations between the mean population densities of melanocytes of the basal layer of the epidermis from one animal to another, the numbers of melanocytes in red and black skin varied in step with one another. The differences in color *within* a single individual, therefore, cannot be attributed to differences in the concentrations of the melanocytes; it is the *mode* of pigmentary activity that is responsible.

Bischitz and Snell (1959) have recently compared the melanocyte densities in the epidermis of the areola, ear, and ventral body wall of two different strains of guinea pigs, of black and red phenotype respectively. Some of their findings for mature adult male animals (Table 1) are in reasonable accord with those of Billingham and Medawar (1953). Bischitz and Snell draw attention to the possibility that the significantly higher melanocyte concentrations in the epidermis of the anterior body wall and areola of their black animals might have been due to genetic differences between their two strains. Certainly the differences in density observed are too trivial to account for color variations. That differences in genotype can affect melanocyte densities is suggested by some observations of Markert and Silvers (1956) on the mouse. For example, they found that there are fewer melanocytes in the ear skin of yellow animals than of co-isogenic black or brown animals.

Besides the guinea pig, the only other species whose pigment cells have been studied quantitatively is man (see Szabó, 1954, 1959; Becker and Zimmermann, 1955; Breathnach, 1957; Staricco and Pinkus, 1957; Pinkus, Staricco, Kropp, and Fan, 1959). The results of the various studies cited, inaugurated by Szabó, are in remarkably good accord (see Table 1). The essential facts which have been established by these investigations will now be outlined.

There are great regional differences in the density of the melanocytes found in the skin of a single individual, and even within the skin of the same region of the body there is great variation in the melanocyte densities found in different individuals. Some of the highest frequency distributions recorded (2,000–2,400/mm^2) are found in the cheek, forehead and penis, whereas the lowest values (800–1,000/mm^2) occur in the skin of the abdomen and back. There is no evidence of a sexual difference in the distribution frequency of melanocytes. According to Szabó (1959) the average density of melanocytes found in all regions of the human body is 1560/mm^2. From some of the data he presents, it can be computed that the total number of melanocytes in the basal layer of the epidermis of an adult man is of the order of 2×10^9. This quantity of pigment cells would weigh slightly more than a gram.

Previous qualitative observations have led to the conclusion that the melanocytes of Indian and Negro skin, like those of albino skin, were no more abundant than those of Caucasian skin from similar regions of the body (Billingham, 1949; Becker, Fitzpatrick and Montgomery, 1952). This conclusion has now been completely confirmed by numerical analyses (Szabó, 1959; Pinkus, Starrico, Kropp and Fan, 1959). In the races of man, as in the color types of guinea pigs, variations in skin color are related, not to differences in melanocyte concentration but to differences in melanocyte activity.

From preliminary studies so far reported it appears that in pathological conditions which have associated changes in skin pigmentation, it is the functional aspect of the melanocytes rather than their numerical incidence which is affected. For example, in both classical Addisonian hyperpigmentation of the skin, and the several varieties of vitiligo, characterized by the appearance of depigmented areas in otherwise normal skin, the melanocyte densities are within normal limits (Becker et al., 1952; Jarrett and Szabó, 1956; Szabó, 1959).

The incidence of melanocytes in relation to that of the Malpighian cells has also been studied by Szabó (1959). His estimates range

TABLE 1

Some estimates of the melanocyte densities in the superficial epidermis of guinea pig and man

Species	Regional Origin of Epidermis	Color or Ethnographic Type	Mean Number of Melanocytes per mm² ± S.E.	References
Guinea Pig	dorsum of ear	black	920 ± 144	Billingham and Medawar (1953)*
	" " "	red	866 ± 101	
	side of trunk	black	420 ± 39	
	" " "	red	392 ± 30	
	dorsum of ear	black	1141 ± 47	Bischitz and Snell (1959)
	" " "	red	1067 ± 75	
	areola	black	831 ± 35	
	"	red	641 + 50	
	anterior abdominal wall	black	305 ± 27	
	anterior abdominal wall	red	165 ± 25	
Man	penis	Caucasian	2,380 ± 280	Szabó (1959)
	cheek	"	2,310 ± 150	
	forehead	"	2,010 ± 210	
	nasal and oral epithelium	"	1,660 ± 130	
	thigh	"	1,000 ± 70	
	abdomen	"	800 ± 40	
	back	"	1,070 ± 100	
	"	Negro	940 ± 60	
	thigh	Caucasian	1,149	Pinkus *et al.* (1959)
	"	Negro	997	

* Billingham and Medawar's data for trunk skin epidermis relate only to the "hill" regions in which melanocytes are actually present, and do not allow for the valley regions in which they do not occur.

from 1:4 in the epidermis of the cheek, where the hills are not separated by large valleys, to 1:12 in the epidermis of the skin of the thigh or arm, where the hill and valley pattern is more highly developed. The melanocytes were found to be more numerous and more evenly distributed in the hills than in the valleys. These findings completely bear out the conclusions of other workers that the mode of branching and incidence of melanocytes is such that each and every basal layer Malpighian cell is in contact with at least one melanocyte end-organ.

VI. EXTRA-EPIDERMAL MELANOCYTES

Although the attention of biologists and dermatologists has, for very obvious reasons, been devoted mainly to the melanocytes of the epidermis, the distribution of these cells is certainly not restricted to this tissue. Indeed, from a purely functional viewpoint the most important melanocytes are probably those responsible for the pigmentation of the choroid, the retina and the iris of the eye, where the significance of the pigment is obvious. In the adult all the intraocular pigment cells are Dopa-negative, although during that period of embryonic life when they are elaborating melanin they give a strongly positive reaction with this substrate and with tyrosine (Miescher, 1921, 1933; Miyamoto and Fitzpatrick, 1957; Fitzpatrick and Kukita, 1959). Masson (1948a) aptly described these transiently melanogenic cells as "continent," since once they have elaborated their quota of pigment they apparently retain it throughout life instead of handing it on to neighboring cells. The demonstration that oxidative enzymes, including a "dopa-oxidase," are present in extracts of bovine ciliary bodies and are associated with pigment granules isolated therefrom (Herrmann and Boss, 1945), and repeated clinical observations that the melanocytes of the choroid or the iris may be-

come neoplastic and give rise to melanomas (Callender, Wilder, and Ash, 1942; Reese, 1944; Wilder, 1948) suggest that the loss of the pigment-forming mechanism in these intra-ocular melanocytes in the adult may not necessarily be complete and irreversible. Although no instances are known in which the melanocytes of the retinal pigmented epithelium have become the primary site of malignant melanomata (Fitzpatrick, Brunet, and Kukita, 1958), there is a hereditary disease, retinitis pigmentosa, in which abnormal depositions of pigment occur in this tissue (Macklin, 1948).

The cytology of the melanocytes of the various ocular tissues is still imperfectly known because of the normally intense pigmentation associated with these cells and their consistently negative Dopa reaction. Whereas the melanocytes of the choroid and iris appear to have the usual branched structure those of the retina have a highly distinctive form. As seen from the outer side they are hexagonal epithelial cells which are in contact with the inner surface of the choroid. Internally, however, the cytoplasm of these cells extends in the form of thin processes between the rods. Thus retinal pigment cells appear to form an epithelium without the cooperation of any other type of cell. These retinal melanocytes also differ from all other melanocytes in two other important respects: (a) the pigment granules (at least in the mouse) are amazingly diverse in size and shape (Markert and Silvers, 1956), and (b) the cells have a different embryological origin, coming from the outer wall of the optic cup instead of from the neural crest. This difference in embryological origin probably accounts for the dissimilarities of the two types of pigment cell, including the fact that the one type appears not to undergo malignant transformation.

In many mammals, including man, the leptomeninges, which may be of neural crest origin (Hörstadius, 1950), commonly exhibit pigmentation, especially in dark skinned individuals. Melanocytes are responsible for this leptomeningeal pigmentation, which has been studied in detail and illustrated by Fitzpatrick and Lerner (1954). These cells are found on the ventral surface of the medulla oblongata and more rarely extend to the region of the olfactory bulb and fissure of Sylvius. They are rather elongate and ribbon-shaped and their processes interconnect to form a syncytium. In the mouse's brain melanocytes also occur in the meninges, particularly between the olfactory and cerebral hemispheres.

The occurrence of melanocytes in at least some areas of the dermis is common to nearly all mammals. Even in man, who has little dermal pigmentation, elongate, ribbon-shaped melanocytes—the Mongollen-Zellen of Bloch (1929)—are consistently found scattered deep in the dermis of localized areas in the sacral region, where the pigment they elaborate is responsible for the so-called Mongolian spots (demonstrable in Caucasians as well as Mongolians). These cells elaborate pigment in embryonic life long before any has appeared in the epidermis. They produce granules darker and coarser than those elaborated by epidermal melanocytes (Becker, 1927). Mongolian spots represent postnatal remnants of a generalized intradermal distribution of melanoblasts characteristic of fetal life, according to Zimmermann and Becker (1955). These spots are present in early childhood but seldom persist into adult life. The so-called blue nevi are the result of the occurrence of compact masses of melanocytes in the dermis and probably are similar in origin to Mongolian spots. In many of the higher primates the uniform bluish-gray color of the greater part of the integument is due to dermally located melanocytes (see Adachi, 1903; Zimmermann and Becker, 1959).

In the ears, soles of the feet, tail, scrotum, muzzle, and genital papilla of rats and mice a considerable part, if not the greater part, of the skin pigmentation is due to the branched melanocytes situated in the dermis but melanocytes are not demonstrable in the dermis of the trunk (Steiner-Wourlisch, 1925; Holmes, 1953; Reynolds, 1954; Markert and Silvers, 1956). Furthermore, dendritic melanocytes are found throughout the connective tissue that encapsulates and subdivides the Harderian gland of the mouse, a gland of epithelial origin (Markert and Silvers, 1956).

Within the body cavity the association of pigment with the reproductive tract has long been known to characterize certain marsupials and differentiate them from other mammals. Melanocytes are found in certain parts of the gubernacular apparatus of the male Virginia oppossum and in the homologous gubernacular tissue of the female. According to Finkel (1945)

these cells first appear adjacent to and in the peritoneum of the ventral body wall, and are observable in the gubernacular tissues considerably before the appearance of melanocytes in the integument. Unlike the pigment cells of the latter, those present in the reproductive tract are responsive to the administration of sex hormones or to castration, androgens and estrogens increasing the total number of melanocytes present in the female round body, and ovariectomy reducing the amount of pigmentation. It is of course, uncertain in such situations as this whether the observed numerical changes reflect absolute changes in the size of the melanocyte population or whether they merely represent changes in the proportion of the population of cells which are elaborating or retaining sufficient pigment to reveal themselves.

It seems quite likely that a careful investigation would reveal the constant association of melanocytes with the reproductive tracts of placental mammals, including man. Boyd (1949), with the aid of a silver impregnation technique, has already demonstrated the presence of an extensive system of dendritic cells in the urinogenital epithelium of rabbit, pig and human embryos. In sheep, melanocytes have been observed in the submucosal connective tissue of the uterus and of the Fallopian tubes, and in the sheaths of the tubules of the epididymis (Grant, 1933).

Among the other organs of mammals in which the occurrence of extra-epidermal melanocytes has sometimes been observed are the parathyroid, nictitans, thymus, ovary, and spleen of the mouse (Markert and Silvers, 1956; Silvers, unpublished), the adrenal medulla and the regional lymph nodes in man (Masson, 1948a), and the adrenal capsule and walls of the pelvic blood vessels of sheep (Grant, 1933).

All the evidence is consistent with the conclusion that irrespective of their location, with the exception of retinal melanocytes, these extra-epidermal melanocytes have all originated from the neural crest. The sporadic or even the regular appearance of these cells in so many different tissues and organs has two important implications; firstly, that the establishment of some form of contact with cells of the Malpighian system or any other type of epithelial cell is not a necessary condition for the awakening of the melanogenic faculty of the melanoblast; and secondly, melanoblasts or latent melanocytes may be constant, yet unrecognized ingredients of many different tissues of the body, only expressing themselves where local conditions are favorable.

There is no convincing evidence that these various extra-epidermal melanocytes manifest cytocrine activity (see Section X) and it may well be that this process can only take place when melanocytes are juxtaposed to cells of the Malpighian system. It is probably significant in this respect that no form of "capping" distribution of pigment granules is associated with extra-epidermal pigmentation. Although terminal expansions of the end-processes of dermal melanocytes have been demonstrated, it is unknown whether they are in contact with neighboring cells. Another unresolved question is whether there is a turnover in extra-epidermal melanocytes, mitotic fission making good the loss of cells by attrition, or whether these pigment cells are long-lived and incapable of dividing.

Even the elementary student of zoology is aware of the great abundance of extra-epidermal melanocytes in the mesenchymal tissues of lower vertebrates, where they are particularly prominent in the walls of the coelomic cavity and of blood vessels and in perineural connective tissue. Overt extra-epidermal pigmentation is more conspicuous in birds than in mammals and in this group is found the supreme example of the phenomenon: in the so-called Silkie bantam fowl, pigment cells permeate all the connective tissues as well as many of the internal organs such as the ovary and even the heart (Bloch, 1929).

VII. THE ORIGIN AND SELF-MAINTENANCE OF EPIDERMAL MELANOCYTES

For nearly half a century two sharply different opinions were held as to the origin of the melanocytes in the epidermis. According to the "transition" theory, strongly supported by Bloch (1929) and still not lacking in adherents (Allen and Spitz, 1954), melanocytes are derived directly from Malpighian cells as a result of functional stimulation and merely represent melanogenically active forms of these cells. Adherents of this interpretation have maintained that each and every Malpighian cell is, in effect, a potential melanocyte and has the

potentiality of assuming the dendritic form and synthesizing melanin when subjected to a melanogenic stimulus (Percival and Stewart, 1930). The alternative view, by no means new (see Ehrmann, 1885), is that epidermal melanocytes are of *extraneous* origin and are functionally different from the neighboring cells of the Malpighian system. Masson (1926) and others (Pautrier, Lévy and Diss, 1928) maintained that they were of nervous origin. In a critical review written as late as 1940 Meirowsky gave it as his opinion that "the central problem in pigment research is the origin and significance of the dendritic cells" (i.e. melanocytes). So far as the *origin* of the mammalian pigment cell is concerned this question has been completely resolved for almost two decades. An elegant and important series of experimental analyses conducted in amphibia (DuShane, 1934, 1935; Twitty, 1936), birds (Dorris, 1939; Eastlick, 1939; Hamilton, 1941), and mice (Rawles, 1940, 1947) clearly established that melanocytes are derived from the neural crest, like the cells of the dorsal root ganglia, the adrenal medulla and other chromaffin tissue, and like the Schwann cells of all peripheral nerves and possibly the cells of the leptomeninges (Hörstadius, 1950). These various experiments, proving the neural crest origin of the pigmented cells in the vertebrates cited, turned upon correlation of the presence or absence of pigment cells in grafts with the morphological development of the neural crest at the time the tissue was excised, and the demonstration that *only* those tissues containing neural crest or migrant cells derived from it could produce pigment. In Rawles' (1940, 1947, 1953) experiments on the mouse, somite tissue with overlying ectoderm was transplanted from C57BL mouse embryos to the coelomic cavity of chick embryos—an environment known to sustain melanocyte development as well as the normal development of skin and hair. If either the neural crest or cells originating from it were absent from the grafts at the time of their excision, the grafts remained pigment free.

By appropriately designed grafting experiments she was able to show that the migratory route of the precursor pigment cells from the neural crest is dorsoventral along the anteroposterior axis and that melanoblasts have reached all body regions of mouse embryos by the twelfth day of gestation—i.e., long before any melanin had been synthesized. Dermal melanoblasts have been identified in 14–15 day mouse embryos, located near the dermo-hypodermal junction (Danneel and Cleffmann, 1954). The mechanism by which the future melanoblasts reach their final and definitive locations in the skin and elsewhere still awaits elucidation. Various possibilities have been discussed by Rawles (1953), who drew attention to the possible significance of the fact that melanocytes are found primarily along surface membranes including meninges, walls of blood vessels, sex and urinary ducts, etc. Weiss and Andres' (1952) demonstration that melanoblasts from very young chick embryos, injected into the blood stream of other very young chick embryos, eventually find their way to anatomically appropriate sites, including the feather follicles, is some indication of the migratory and "homing" capacities of these cells.

Since 1948 Zimmermann and his associates (Zimmermann and Cornbleet, 1948; Zimmermann, 1954; Zimmermann and Becker, 1955, 1959) have been conducting a thorough study of the melanoblasts and melanocytes in fetal Negro skin. They have identified and figured precursor stages of melanoblasts containing argentaffin granules in the dermis of fetuses in the tenth week of development, and report that a few epidermal melanocytes were present in the eleventh week, the numbers increasing sharply between the twelfth and fourteenth weeks, indicating a rapid influx of cells. Population densities of 800–1000 melanocytes/mm^2 had become established before the end of the thirteenth week.

Although division stages of melanocytes are difficult to find, probably because of the relatively small number of these cells present in transverse histological sections of skin, mitoses have been observed and figured complete with chromosomes in both adult skin (Billingham, 1948; Masson, 1948a; Pinkus, 1949; Becker, Fitzpatrick and Montgomery, 1952) and embryonic skin (Menge, 1955).

Melanocytes do not lose their pigment during division though their processes normally retract almost completely. This evidence appears to provide little justification for considering that the generative cell of the pigmentary system is a non-pigmented stem cell or melano-

blast which differentiates into a melanocyte that is no longer capable of division (Medawar, 1953). Melanocytes as such are a race of cells sui generis, being reproductively independent of the Malphigian cells (Masson, 1948a).

VIII. THE FATE OF EPIDERMAL MELANOCYTES

So far we have considered epidermal melanocytes only as they occur in the basal layer of the epidermis, juxtaposed to the papillary layer of the dermis. Since they are a race of cells sui generis, there are two possible fates open to them. Either (a) the progeny of their mitotic fissions remain in the basal layer, retaining their powers of division and melanogenesis, and divisions occur only frequently enough to make good loss through occasional attrition or accident, or (b) melanocytes are like Malpighian cells, constantly proliferating, and some of their division products participate in the dynamic stratigraphy of the epidermis, eventually becoming lost as squamous cells from the surface of the stratum corneum. This view was first suggested by Redslob (1922) on the basis of his studies on the pigmentation of conjunctival and corneal epithelium and subsequently supported by Masson (1948a) from his extensive studies on the melanocytes of skin.

In a classic paper of 1868 Langerhans carefully described and figured branched cells—known as "Langerhans" cells—in the higher strata of the epidermis of human skin which had been treated with an acid solution of gold chloride. He considered that these cells were intra-epidermal nerve endings. These "high level" branched cells—so designated since they are not found in the basal layer of the epidermis—can be demonstrated with varying degrees of consistency in the epidermis of man, mouse, guinea pig, etc. by a variety of gold impregnation techniques, including those of Gairns (1930) and Cohnheim (Fig. 6). The significance of the Langerhans cells is still highly controversial. Some authorities have denied that they are cells at all, regarding them as artifacts (Rawles, 1955). The hypothesis that they have a sensory function was strongly upheld in an extensive review by Ferreira-Marques (1951), who argued that they constitute an intra-epithelial system of exteroceptors connected with the nervous system. According to him, there are on the average 670 Langerhans cells per mm^2 of epidermis—a figure which is comparable with the number of melanocytes found per mm^2 in human skin from some regions of the body.

In addition to the branched cells demonstrable by gold impregnation techniques, similar wiry, angular, non-pigmented branched cells are also revealed in sheets of pure epidermis removed enzymatically from weakly pigmented skin and subjected to prolonged supra-vital staining with brilliant cresyl blue (Billingham and Medawar, 1953; Reynolds, 1954). Furthermore, methods appropriate for showing "clear cells" in the basal layer of the epidermis also reveal the existence of clear cells at more superficial levels. Their cell bodies are often somewhat elongated and angular, and proximal portions of processes issuing from them are frequently visible.

On the basis of a comprehensive study Billingham and Medawar (1953) have argued cogently that the Langerhans cells revealed by gold impregnation, the "high level" branched cells which may be supra-vitally stained, and the high level clear cells are merely so many different preparation images of the same cell. A similar conclusion has recently been reached by Fan, Schoenfeld, and Hunter (1959) from studies on guinea pig skin. Apart from the fact that they never possess pigment granules, have not been observed in the process of dividing, and are not normally Dopa positive, high level branched cells and melanocytes resemble each other closely in innumerable ways. Their size and shape is comparable; both are nucleate and have well-defined perikarya which give off dichotomizing branches which weave between the more or less rounded cells of the Malpighian lineage, and end in terminal buttons applied to the latter. Occasionally there may be fusion of branches between neighboring cells. The spacing of the high level cells and the melanocytes within the epidermis is such that their dependent territories lie contiguous, and finally, as seen in ordinary transverse sections as clear cells, both have a clear nonbasophilic cytoplasm which is difficult to fix properly and collapses around the nucleus in a distinctive manner.

Actual estimates of the numbers of gold-impregnated high-level cells in guinea pigs' ear skin correspond closely enough to estimates of

the number of basal layer melanocytes in this material to justify the hypothesis of a one-to-one correspondence between the numbers of the two types. The number of high level dendritic cells in the epidermis is therefore entirely consistent with Masson's (1948a) and Billingham and Medawar's (1953) belief that they are effete melanocytes derived from the basal layer in the process of being eliminated (see Fan, Schoenfeld and Hunter, 1959). Further supporting evidence for this hypothesis is the fact that the high level branched cells are not demonstrable in epidermal epithelia which lack melanocytes, such as guinea pigs' tongue and normal cornea. However, if under any pathological conditions the cornea becomes vascularized, pigment granules do appear in its epithelium and cells of Langerhans are demonstrable (Redslob, 1922). Presumably the melanocytes responsible for this pigment are of migratory origin from the limbus, the epithelium of which is always pigmented even in Caucasians.

There is, therefore, a considerable body of circumstantial evidence that melanocytes are, like Malpighian cells, expendable or squamous cells. As soon as they embark upon their upward journey of degenerative specialization they lose their capacity to react with Dopa and they lose their pigment granules, presumably since they have handed them on to Malpighian cells. Eventually, they are lost from the surface. The weakness of this interpretation, common to all hypotheses of cellular transformation in histology, is that it rests entirely upon circumstantial evidence. It may be added that the evidence that melanocytes are expendable cells is almost, if not every bit, as convincing as that supporting the accepted view that Malpighian cells are expendable. To clinch this matter the production of a mitotic balance sheet for melanocytes is urgently required.

Kropp (1957) has reported that melanocytes play a purely passive role during the enforced regeneration of human epidermis that follows stripping off the stratum corneum with plastic tape. This evidence suggests a high degree of autonomy on the part of the pigment cell. It would be very interesting to know whether under the conditions of this study there was a decline in the number of high level branched cells in the epidermis. It may be added that the epidermal hyperplasia which follows the healing-in of a skin graft *does* increase the mitotic frequency in melanocytes (see Billingham, 1948).

The significance of the fact that *high level* branched cells *are* demonstrable by several techniques in the superficial epidermis of white spotted areas of recessively spotted guinea-pigs and mice (Billingham and Medawar, 1953; Reynolds, 1954) is highly provocative and controversial since, despite considerable effort, no one as yet has been able to demonstrate the presence of clear cells or amelanotic melanocytes in the basal layer of this tissue. There are two possibilities: either (1) as Billingham and Medawar (1953) have argued, these high level branched cells are the effete end products of congenitally amelanotic melanocytes whose presence in the basal layer has to be *inferred* (inability to reveal them may be attributed, at least in part, to their lack of the melanogenic enzyme system); or (2) as some investigators maintain, there are no melanocytes in the basal layer of white spotted regions, and the high level branched cells of the epidermis as a class are unrelated to melanocytes (see Section XII on pigment spread). Silvers' (1957b) report that aurophilic dendritic cells are demonstrable in murine skin experimentally deprived of its neural crest component lends some support to this possibility.

IX. MELANOCYTES IN HAIR FOLLICLES AND THEIR RELATIONSHIP TO THE MELANOCYTES OF THE SUPERFICIAL EPIDERMIS

The melanocyte system of mammalian skin consists of two anatomically and, at least to some extent, physiologically distinct parts: that which we have just considered, belonging to the basal layer of the superficial epidermis, and that belonging to the hair bulbs and responsible for the pigmentation of the hair (Fig. 5). Like the melanocytes of the superficial epidermis, those in the hair bulbs have long been known. For example, Ehrmann (1885) illustrated them very clearly. It is now generally agreed that when hair is actively growing, melanocytes of the matrix supply pigment granules to the Malpighian-type cells of the upper bulb which are to become the cells of the medulla and of the cortex, presumably as a consequence of their melanogenic and cytocrine activity.

Only in actively growing hairs are Dopa and

tyrosine oxidase activities generally detectable (Fitzpatrick, Brunet and Kukita, 1958), the appearance of these enzymes coinciding with the presence of pigment granules in the melanocytes, and the strength of the reactions increasing with the increase in the population of these cells during anagen (see Chase, Rauch and Smith, 1951). The fate of the melanocytes in telogen or resting hair follicles is still unresolved and controversial on account of the fact that these cells apparently lose their morphological characteristics, their pigment, and their oxidase activity (Kukita, 1957). However, Quevedo and Isherwood (1958) in irradiation studies on murine skin have demonstrated a localization of melanocytes in the epithelial germ region of telogen hair follicles similar to that reported by Taylor (1949) for the rat. In other species, including man and dog, it appears that telogen melanocytes are localized in the dermal papillae (Danneel and Weissenfels, 1953; Weissenfels, 1954).

Presumably during hair growth the effete melanocytes from the hair bulbs are incorporated into the hair shafts, for this would appear to be the only pathway open to them. Curiously enough one can seldom, if ever, identify effete branched cells in hair shafts, although concentrated clumps of pigment granules are not uncommon and may represent the terminal caps of melanocyte processes. Metchnikoff (1901) appears to have been more successful, since in a study of the graying hairs of men and dogs he observed branched nucleate pigment-containing cells in the shafts which he naively interpreted as phagocytes in the process of depigmenting the hairs. Apparently on the basis of this belief, Metchnikoff was one of the few investigators prepared to accept the possibility of a person's "going gray overnight" (see Ephraim, 1959). This absence of identifiable melanocyte fragments in the hair shaft is probably the result of the much more profound biochemical and morphological transformations that the cells undergo in the keratogenous zone of a follicle than in the more superficial strata of the epidermis.

The question arises as to the source of melanocytes for each succeeding hair generation. The possibilities are (a) they may be mitotic descendants of the previous follicle population of melanocytes or re-activated melanocytes which have undergone a period of enforced inactivity during which they may have become rounded off, lost their pigment, and become temporarily incapable of melanogenesis; (b) they may arise from melanoblasts which migrate into the papilla from the dermal tissues surrounding the base of the follicle, as suggested for feathers by Foulks (1943); (c) they may originate from a papilla reservoir of melanoblasts which is augmented periodically by cells migrating in from the surrounding tissues as Cock and Cohen (1958) have recently proposed for feathers; or (d) they may arise from unpigmented stem melanoblast cells in the epithelium. Some of these possibilities are discussed by Chase (1958). Although not conclusive, in the opinion of the present reviewers, the first possibility is most consistent with the evidence at present available, particularly that relating to the capacity for self-maintenance of the melanocytes of the superficial epidermis.

Although the hair bulbs and the basal layer of the epidermis are continuous through the outer root sheath, the density of melanocytes falls off sharply from the follicle base towards its opening, and Billingham and Medawar (1948a) found that these cells were either completely absent from the follicle neck in the region where the sebaceous glands enter it, or are so sparse that they do not form a contiguous system. In most mature follicles they are entirely absent from this region of the neck.

The pigmentary activity of the hair bulbs may frequently differ both qualitatively and quantitatively from that of the superficial epidermis. For example, in white human beings dark hairs may grow in almost colorless skin. In mice and rabbits, the melanocytes of the superficial epidermis of trunk skin are normally non-melanogenic, whereas those in the follicles may be very active. The normally amelanotic melanocytes of the superficial epidermis of trunk regions of pigmented mice can be stimulated to produce melanin and so reveal themselves, when the skin is painted with irritants, such as turpentine and acetone (Reynolds, 1954) or 5,9,10-trimethyl-1,2-benzathracene (Burgoyne, Heston, Hartwell and Stewart, 1949), which cause epidermal hyperplasia. In red-and-black patched guinea pigs, red hairs may issue from black skin in the transitional zone between red and black areas, and genetic studies in the

guinea pig have shown that the melanocytes of the two subsystems may be affected differently by certain genes (Russell, 1939). Furthermore, the melanocytes of hair follicles may cease to function, as in graying of hair, whereas those of the superficial epidermis of the same skin retain their ability to produce pigment on appropriate actinic stimulation, as in sun tanning in Caucasians, or normally as in gray-haired Negroes.

If the melanocytes of a hair follicle are destroyed by ionizing radiations (Chase and Rauch, 1950) or by intense local cooling of the skin (Taylor, 1949), the hair follicles are permanently affected so that they subsequently only give rise to white hairs. These findings constitute strong evidence that the loss of melanocytes from mature follicles is not normally made good by subsequent migrations from the superficial epidermis or elsewhere.

Despite their normal separateness, the members of these two systems of melanocytes are fully interchangeable. If the superficial epidermis is removed from an area of hair-bearing skin of a guinea pig so that the bases of the follicles are left behind, the epidermis will be reformed from epithelium and melanocytes of migratory origin from the follicles (Pepper, 1954). Similarly, if a suspension of autologous viable epidermal cells, prepared from pigmented skin of guinea pigs or rats, is "seeded" onto a defect prepared in a white hair-bearing region by excising the superficial dermis and epidermis, the grafted melanocytes become incorporated into the matrices of the transected follicles, so that when these regenerate pigmented hairs are produced (Billingham and Medawar, 1950b; Pepper, 1956).

X. THE SECRETORY ROLE OF MELANOCYTES

Once it became recognized that the melanocyte is the only seat of melanogenesis in the epidermis it followed that the pigment present in Malpighian cells must necessarily be of secondary origin. The mode of branching of melanocytes, the termination of their branches as end-caps or thickenings intimately applied to the upper poles of the Malpighian cells, and the predominantly polar distribution of pigment granules *within* these cells provided strong circumstantial evidence that these granules are in some manner "secreted" into the cytoplasm of Malpighian cells. This conclusion has been reached more or less independently and repeatedly for the different vertebrate classes. Some of the older literature bearing upon this is cited by Masson (1948a). In salamanders, according to Stearner (1946) the processes of the finely branched "melanophores" actually penetrate many of the surrounding epidermal cells, appearing to break up within the latter to form a cap over the outer side of the nucleus. Witschi and Woods (1936) from careful histological studies had no doubt that the melanocytes in the stratified epidermis of the bill of the sparrow hand on pigment to the epidermal cells, but they were unable to decide whether the branches of the melanocytes actually penetrate the epidermal cell bodies. Among the more recent workers on mammalian skin who have found what they regard as convincing evidence that melanocytes hand on melanin to epidermal cells across the end processes are Finkel (1945), who studied the pigmentation of the scrotal skin of the ground squirrel; Billingham (1948); and Masson (1948a). We are particularly indebted to Masson (1948a) for the special term "cytocrine" activity to describe this unique process of transfer of a formed secretory product from one cell directly into the cytoplasm of another. At present the actual mechanism of this transfer process is unknown: it may be a passive inoculation or an active ingestion, for pinocytosis has been described in Malpighian cells in tissue culture (Lewis, Pomerat and Ezell, 1949) and it has long been known that melanin granules are actively taken up by epithelial cells in vitro (Matsumoto, 1918; Smith, 1921, 1925).

Certain morphological similarities between melanocytes and some types of cell in the central nervous system have already been commented upon. Witschi and Woods (1936) have drawn attention to the fact that even the secretion of pigment granules into epidermal cells across the end process of melanocytes is singularly reminiscent of the process by which nerve cells stimulate the peripheral affectors.

Whatever other role melanocytes may fulfill, they must be considered predominantly as unicellular melanin-secreting glands (see Hirsch, 1939). It is interesting to note that melanocytes, when seen as clear cells in transverse sections of normal human epidermis, have on at least

one occasion probably been mistakenly identified as unicellular sebaceous glands because, under certain pathological conditions, it appears that lipid droplets may accumulate in their cytoplasm (Wolff, 1951; Lloyd, 1951).

There have been few attempts to study the organization of the cytoplasm of melanocytes as seen in thin transverse sections of skin, probably because of the dual problems of identification and of satisfactory fixation. Instead, a considerable amount of attention has been devoted to malignant melanomas, now generally accepted as melanocyte tumors, which in man are well known for their high malignancy and ability to metastasize.

At least four different origins have been postulated for melanin granules within the protoplasm of the melanocyte. That the nucleus is a site of origin of a progenitor substance of melanin, or of melanin itself is a hypothesis which formerly was well supported (Ludford, 1924; Meirowsky, 1940; Meirowsky and Freeman, 1951). Quite a strong case has been made out and still exists for the mitochondrial origin of pigment granules, initiated by Reyni's (1924) study of fixed and stained sections of the retinal epithelium of the chick embryo (see also Makarov, 1929; Danneel, 1936). More recently Dubuy, Woods, Burk and Lackey (1949a, b) and Woods and Hunter (1959) have given further support to this hypothesis by cytological studies and biochemical investigations of the oxidase activities of the cytoplasmic particulates of the S 91 and Harding-Passey transplantable mouse melanomas. These workers have suggested on the basis of their findings that melanin granules are variant forms of mitochondria.

The Golgi apparatus as the cytological origin of melanin granules was first proposed by Hirsch (1939), who probably was also the first to compare melanin-formation with a glandular secretion. This hypothesis has recently been supported by Güttes (1953) from a study, based on paraffin sections, of the origin of pigment in the eyes of rabbit and chick embryos.

Since the size of both melanin granules and mitochondria are so near to the limit of its resolution, the ordinary light microscope has not been very informative about their structure. Recently, however, both isolated melanin granules and the melanocytes themselves, as seen in exceedingly thin sections of human skin and of the bulbs of hair follicles plucked therefrom, have been subjected to the scrutiny of the electron microscope with considerable success, notably in the hands of Barnicot and Birbeck and their associates (Barnicot, Birbeck, and Cuckow, 1955; Birbeck, Mercer, and Barnicot, 1956; Barnicot and Birbeck, 1958, 1959). Electron microscopy of intact or sectioned melanin granules, isolated from pigmented hair by mild chemical or enzymic procedures, has established a general though not entirely regular relationship between granule size and hair color, confirming the conclusions of earlier workers that the granules in darker hair or feathers are larger than in lighter ones, and that there is considerable variation in size within the granule population from a single individual.

As seen in sections with the electron microscope, melanocytes are distinguishable from Malpighian cells by the same sort of characteristics that differentiate well-fixed clear cells from their neighbors in orthodox sections, and the proximal portions of some of the processes can usually be recognized. Birbeck, Mercer, and Barnicot (1956) have drawn attention to the fact that in broad outline the cytoplasmic organization of the follicular melanocytes resembles that of other secretory cells. These melanocytes appear to have a definite polarity, usually containing a compact cluster of ergastoplasmic membranes proximal to the dermal papilla and a differentiated area distal to the nucleus which frequently contains numerous filamentous mitochondria together with many small vesicles. Although the center of this zone is stated to be without melanin granules, peripheral small vacuoles surrounded by fine shells or containing convoluted strands are confidently identified as early stages in melanin granule formation by these workers. They argue that the granules apparently start as hollow vacuoles within which a tenuous material appears, usually in the form of a folded filamentous matrix. The latter then undergoes rapid thickening by deposition of denser material, presumed to be the melanin polymer. Considerable support for this interpretation comes from their findings that in the follicle melanocytes of albinos which have minimal amounts of melanin granules, this increase in density does not occur although the basic hollow vacu-

oles containing tenuous material are identifiable. No evidence of a nuclear extrusion of melanin or of any material was obtained (see also Weissenfels, 1956), nor did the evidence suggest that the pigment cells originated by mitochondrial transformation. The concentration of mitochondria around the melanogenic zone left open the possibility that these organelles may play some role in pigment formation. These workers conclude that the Golgi material is the most likely source of the melanin. The melanogenic zone of the melanocytes of the superficial epidermis is stated to be smaller and less compact than in follicular melanocytes.

In a careful study on the melanoblasts of Silkie bantam chick embryo tissues cultured in vitro, Weissenfels (1956), employing conventional, phase-contrast, and electron microscopy, concluded that the pro-pigment granules originated from spherical formative regions located peripherally in the cytoplasm of the melanoblasts which were quite distinct from the Golgi system and which he was unable to relate to any of the known cytoplasmic structures. Like Dalton and Felix (1953), he feels strongly that the theory of the mitochondrial origin of melanin granules lacks adequate cytological supportive evidence.

A detailed account of current views on the biochemistry of melanogenesis is beyond the scope of this article, especially since excellent reviews are available (Lerner and Fitzpatrick, 1950; Fitzpatrick and Kukita, 1959; Fitzpatrick, Brunet and Kukita, 1958; Mason, 1955, 1956).

Bloch's (1927) opinion that melanin is formed by the oxidation of 3,4-dihydroxyphenylalanine (Dopa) by a specific Dopa-oxidase remained securely entrenched for a long time. Indeed it even received what appeared to be some indirect support from various directions. For example, despite their widespread distribution in plants and lower animals, the existence of tyrosinases in mammalian tissues remained very dubious. Moreover, Raper (1927, 1932) in a series of important studies on the aerobic oxidation of tyrosine to melanin in the presence of tyrosinase derived from meal worms, which laid the foundations of the biochemistry of melanogenesis, had found that Dopa is an early intermediary product.

The first serious challenge to Bloch's view came in 1942 when Hogeboom and Adams, studying extracts of mouse melanoma tissue, demonstrated the existence of a tyrosinase in mammals for the first time. Subsequent investigators, employing a variety of techniques, established the presence of tyrosinase in the skin of rats (Spoor and Ralli, 1944), mice (Foster, 1951; Foster and Cook, 1954), fetal guinea pigs (Foster, 1952), and men (Becker, Fitzpatrick and Montgomery, 1952; Szabó, 1957; Breathnach, 1958), and in human malignant melanomas (Fitzpatrick and Szabó, 1959).

In the light of recent investigations (see Fitzpatrick and Kukita, 1959) it appears almost certain that only a single, copper-containing enzyme complex, tyrosinase, is involved in the first two steps of the conversion of the colorless amino acid, tyrosine, to melanin: first, the hydroxylation of tyrosine to Dopa, and second, the oxidation of Dopa to Dopa quinone. The final product of this enzymatic oxidation process, melanin, is a protein conjugate formed by the coupling of a quinonoid polymer, indole-5,6-quinone with protein. The fact that melanin granules isolated from melanoma tissue actually contain tyrosinase as well as cytochrome oxidase and succinic dehydrogenase (Herrmann and Boss, 1945) might account for their apparent ability to grow in size even after they have left the cytoplasm of the melanocytes and have taken up residence in cells of the Malpighian system (Chase, 1954b)—provided that tyrosine is available.

Among the disadvantages of Dopa as a substrate for cytochemical studies on melanogenesis and the revelation of melanocytes are its instability and the fact that it is readily oxidized to Dopa melanin by oxidizing systems other than tyrosinase. As Szabó and Fitzpatrick (1959) point out, tyrosine is oxidized to melanin only by tyrosinase present on cytoplasmic melanin granules. However, the conversion of tyrosine to melanin is characterized by a variable lag period, which in the presence of low concentrations of tyrosinase is prolonged to such an extent that the enzyme cannot be detected using tyrosine as a substrate. With Dopa, on the other hand, there is no lag period. In the melanocytes of growing hair follicles which contain abundant tyrosinase, and in melanocytes of Caucasian skin which has been stimulated with thorium-X, this enzyme is readily detectable with either Dopa or tyrosine (Fitzpatrick and Szabó,

1959). However in the epidermis of unstimulated Caucasian skin there is a considerable regional variation in the number of melanocytes which are tyrosine-positive (Szabó, 1957). Although strong positive reactions were usually obtained in areas normally exposed to solar radiation, it was observed that positive reactions could also be obtained from melanocytes in the skin of unexposed regions such as the external genitalia and nasal and oral epithelia.

To circumvent the difficulty of appraising the intensity of the tyrosinase reaction in heavily pigmented melanocytes, Kukita and Fitzpatrick (1955) have ingeniously employed labeled tyrosine containing C^{14} as a substrate. The radioactive melanin formed is detected on the basis of the silver grains produced in a photographic emulsion.

This autoradiographic technique has also been utilized in important in vitro studies on chick embryonic tissues by Markert (1955). His findings indicated that whereas tyrosine uniformly labeled with C^{14} did become incorporated into melanin in the melanocytes, tyrosine which had been labeled only on its side-chain was not. In his opinion this observation casts doubt upon the generally accepted scheme for melanin formation.

Although tyrosine is involved in the formation of both melanin and phaeomelanin (Fitzpatrick, Brunet and Kukita, 1958) and both substances appear to be quite closely related chemically, Fitzpatrick and Kukita (1959) have recently questioned whether tyrosine is the natural chromogen of phaeomelanin. These workers cite some of their recent findings in support of a tentative hypothesis that phaeomelanin may be formed as a result of the oxidation of an ortho-aminophenol by Dopa quinone under the influence of a genetically controlled switch mechanism.

XI. THE GENETIC CONTROL OF MELANOCYTE ACTIVITY

Long before the anatomical basis of melanogenesis had been agreed upon geneticists were making good progress in elucidating the genetic determinants of mammalian coat coloration, basing their studies upon the assumption that the various patterns of pigmentation in hair are chronological records of the final results of synthetic processes occurring in the follicle bases. Their analyses depended essentially upon the appraisal of quantitative and qualitative differences in the pigmentation found in the fur of different phenotypes.

Since the effect(s) of a particular genetic locus can only be recognized on the basis of variations (alleles) from wild type produced by mutations, development of this work depended upon obtaining mutants and observing their effects when combined with various other coat color determinants. A thorough systematic investigation, therefore, required the initial production of different stocks of animals, each of which could be defined in terms of its constant coat-color genotype. Various types of comparison were made between the members of different stocks and, by appropriate matings, the expression of various mutant genes on different backgrounds was assessed and various hypotheses put forward concerning possible underlying mechanisms.

One interesting extension of these analyses entailed an investigation of the capacity of hair bulbs, or even of skin extracts, of different genotypes to bring about the oxidative blackening of Dopa (Russell, 1939; Russell and Russell, 1948; Ginsburg, 1944). Work conducted along these lines has been reviewed by Wright (1941, 1942) and by Little (1958).

As soon as the extra-epidermal origin of the melanocyte and its melanin-secreting role had been unequivocally established it became obvious that at least some of the genes affecting hair color might be acting *indirectly* upon the melanocytes via the milieu of the follicles. Only by combining melanocytes of one genotype with follicles of another could this possibility be investigated. To do this required the development of inbred and coisogenic color lines, the latter being stocks differing from one another with regard to a single gene concerned with pigmentation.

Some Genetic Loci Affecting Pigmentation in Mice

Because of the availability of a large number of coat color mutants and inbred strains, and also the facility with which the requisite stocks could be produced, the genetics of pigmentation has been more thoroughly worked out in the mouse than in any other species. At present in the mouse at least 25 loci, involving more than

35 genes, are known which affect coat and/or eye pigmentation (see Grüneberg, 1952, 1956). In addition 13 other loci are concerned with white spotting. Within this impressive array of genetic loci concerned with melanogenesis or its absence, no less than 20 are pleiotropic (i.e. have other effects—see below). A full account of what is known about the genetics of coat or skin coloration is beyond the scope of this article. However, the following account of the roles of a few well studied loci in the mouse will illustrate at least in principle how the activity of melanocytes is governed genetically (see Table 2).

Comparative histological studies of pigment in the hair septules in various gene substitutions, initiated by Werneke (1916) and greatly extended by Russell (1946, 1948, 1949a, b), have shown that the differences in appearance of coat color mutants depend upon a large number of different variable pigmentation attributes including the nature of the melanin granules, their size, shape, number and arrangement. Consequently some of the genes concerned with melanogenesis must produce their effects by alteration of one or more of these attributes.

The action of genes at the agouti locus (see below) determine the kind of melanin which will be produced by the melanocytes of the hair bulbs, i.e. whether it is eumelanin (black, brown), phaeomelanin (yellow), or both as in the agouti pattern.

The four allelic genes at the albino locus (C, c^{ch}, c^{e}, and c) appear to control, quantitatively, without affecting its nature, the general level of pigmentation, suggesting that this locus controls the formation or availability of some substance essential for the formation of all pigment.

The main effect of brown (bb)/black(B-) substitution at the so-called B locus is a qualitative change occurring only in eumelanotic regions, whereas pp/PP substitution alters both the size and shape of the pigment granules as well as reducing the level of pigmentation. It is interesting, however, that the recessive condition, pp, has no effect on the size of yellow granules.

TABLE 2

Action of some major genes concerned with melanogenesis in the mouse

Locus	Gene Symbols	Name of Genes	Site of Action	Probable Action in Melanoblast Differentiation
A	A^{y}	Yellow	Hair follicle	Polymerization of melanin
	A^{w}	Yellow-bellied agouti		
	A	Agouti		
	a^{t}	Black-and-tan		
	a	Non-agouti		
B	*B*	Black	Melanoblast	Polymerization of melanin
	b	Brown		
C	*C*	Colored	Melanoblast	Melanin synthesis on pigment granule
	c^{ch}	Chinchilla		
	c^{e}	Extreme dilution		
	c	Albino		
D	*D*	Non-dilute	Melanoblast (but expressed only in suitable cellular environments)	Melanocyte morphology
	d	Dilute		
Ln	*Ln*	Non-leaden	Melanoblast (but expressed only in suitable cellular environments)	Melanocyte morphology
	ln	Leaden		
P	*P*	Colored eye	Melanoblast	Basic protein structure of melanin granule
	p	Pink eye		

Finally, the main effect of substitution at either one of two independent loci, dilute (*dd*)/non-dilute (*D-*) or leaden (*lnln*/*LnLn*), is alteration of the pattern of the deposition of pigment granules in the cells of the hair shaft so that they form large granular clumps, unevenly distributed among the septules.

Action of Genes at the Agouti Locus

The agouti pattern of hair pigmentation has been described in the mouse by Dry (1928), Kaliss (1942), and Russell (1949b), and in the rabbit by Danneel (1947, 1948) and Cleffmann (1953). The effects of the agouti series of genes of the mouse upon pigment lend themselves particularly well to experimental analysis since, through substituting different alleles at this one locus, the coat can be varied from all black (*aa*) to all yellow (A^{y}-). Between these extremes are the agouti (*A-*), yellow-bellied agouti (A^{w}-), and black-and-tan (a^{t}-) types. Over most of the body, the agouti mouse exhibits a yellow banding of the otherwise black or brown hair—i.e. the main eumelanin coloration is interrupted by a phaeomelanotic band; the yellow-bellied agouti mouse has a banded dorsum and yellow looking ventrum; and the black-and-tan animal a black dorsum and yellow ventrum. The dominance relationships between these various alleles differ between the dorsal and ventral surfaces of the animal, with ventrality appearing to favor the production of yellow pigment.

By transplanting histocompatible (see Snell, 1957; Billingham and Silvers, 1959) skin grafts from near term or neonatal donors to newborn recipients which differed in respect to the nature (agouti locus constitution) and intensity (other loci) of their future pigmentation, Silvers and Russell (1955) and Silvers (1958b, c) have studied the behavior of melanoblasts of all 5 agouti locus genotypes mentioned above in genetically alien follicles. In these experiments host melanoblasts entered and became incorporated in the developing follicles of the graft, thus enabling the investigators to determine whether the genes concerned were acting intrinsically *within* the melanocytes, or whether they were acting via the follicular environments.

It was found for example, that when genotypically black melanoblasts, *aa*, migrated into hair bulbs of a skin graft which, although (phenotypically) non-pigmented, was genetically yellow ($A^{y}ac^{c}c^{c}$), yellow pigment was produced. The typical agouti hair pattern resulted when genotypically yellow (A^{y}-) or black (*aa*) melanoblasts invaded dorsal agouti (but non-pigmented) hair bulbs. Similarly when black (*aa*) and yellow (A^{y}-) melanoblasts invaded *dorsal* a^{t} (but nonpigmented) hair follicles they produced black hairs characteristic of the dorsum of black-and-tan animals. When these melanoblasts invaded *ventral* hair follicles of the same genotype, intensely pigmented yellow hairs with black bases and some all-yellow hairs (characteristic of the ventrum of intensely pigmented black-and-tan animals) were observed among the white hairs of the graft.

These results, therefore, indicate that the agouti locus genotype of the *receiving hair follicle* determines whether eumelanin or phaeomelanin or both (the agouti pattern) will be produced. The results with black-and-tan and yellow-bellied agouti further demonstrate that the expression of genic activity is dependent not only upon the genotype of the follicular environment but also upon the location of this environment—i.e. whether it is on the dorsum or ventrum of the animal. In a^{t}- and A^{w}- genotypes ventrality and dorsality are not important per se, but together with their genetic constitution they present different follicular environments which affect the expression of adjacent cells—in this case melanocytes.

These results are in accord with the fact that neural crest cells from genotypically yellow embryos not only differentiate into eumelanin-secreting melanocytes in the coelom of the chick or in the spleens of phenotypically different murine hosts (Silvers, 1957a), but also in those regions of yellow mice where melanin pigment is normally found outside of the hair, e.g. in the Harderian gland or eye (Markert and Silvers, 1956). The intrinsically determined capacity of the melanoblasts of all genotypes, therefore, is apparently to produce eumelanin; but in the local milieu of "physiologically" appropriate hair bulbs they produce phaeomelanin.

Despite apparently great qualitative differences in the nature of yellow and black pigment a rather rapid change occurs from one pigment type to the other along agouti-banded hair shafts. Kaliss (1942) observed a gradual darkening of granules from septule to septule rather

than a sudden change from yellow to black. Cleffmann (1953) carried this work further in studies of the hair follicle melanocytes of agouti hairs in the rabbit. It was found that all the pigment cells underwent a gradual transition with respect to the nature of their pigment content. It therefore appears that in each agouti-series genotype there is a uniform population of melanoblasts in the follicles whose capacities vary with conditions. Furthermore, Cleffmann's observations indicate that a single melanocyte can elaborate *both* eumelanin and phaeomelanin. This is in contrast with findings from studies on avian melanocytes. Here it would appear that while each melanoblast has the genetic capacity to produce either red or black pigment, once the melanoblast becomes "fixed" as to the kind of melanin it will produce, it cannot change to the opposite type (Danforth, 1937; Hamilton, 1941; Nickerson, 1946; Trinkaus, 1948).

Action of Genes at the B, C, D, Ln and P Loci

The experimental design used to explore gene action at the agouti locus has also served to investigate whether other genes concerned with pigmentation act *within* the melanoblasts or act through the cells composing their environment. In the agouti study described above, it was found that the genotype of the receiving follicle in the graft at the *C* locus had no effect on the immigrant melanocytes of host origin, the intense pigmentation of the host melanocyte being fully expressed in both *cc* (albino) and $c^{e}c^{e}$ (extreme dilution) skin grafts. This locus, therefore, evidently controls the activity of some enzyme essential for melanogenesis, and this enzyme, when present, is located within the melanoblasts themselves.

The *B* and *P* loci also apparently produce their effects on melanocytes independently of the tissue environment since the granule attributes of melanocytes determined by these loci are unaffected when these cells are incorporated into hair bulbs of different *B* or *P* constitutions (Reed and Henderson, 1940; Silvers, 1957a, 1958c). While the genes at the *B* locus are most probably concerned with melanin polymerization, those at the *P* locus are concerned with the shape of the granule and presumably change the protein matrix of the granule within the melanocyte (Markert and Silvers, 1956).

As mentioned above, presence of the genes *dd* (dilute) or *lnln* (leaden) result in coat color deviations which are similar in effect and in cause (Markert and Silvers, 1959). The fur of *dd* and *lnln* genotypes appears lighter in color than their corresponding dominant types, hinting that dilution of the melanin pigment of the hair has occurred. However, on microscopic examination this paler color is seen to result primarily from the clumped distribution of the melanin granules, and this distribution in turn reflects alteration in the morphology of the melanocytes concerned (Markert and Silvers, 1956). In "leaden" and "dilute" genotypes the melanocytes have fewer and finer dendritic processes and hence the pigment granules are largely clumped around the nucleus in the body of the cell. This type of pigment cell has been designated "nucleopetal" as opposed to the more familiar melanocytes which are "nucleofugal" (Markert and Silvers, 1956).

To determine the site of action of the genes at the *D* and *Ln* loci Markert and Silvers (1959) transplanted embryonic tissues containing melanoblasts from *dd*, *D-*, *ln ln* and *Ln-* genotypes into the anterior chamber of the eye of adult albino or pink-eyed (*pp*) animals having the same or different *Ln* and *D* constitutions as the graft. Whereas in all cases donor melanocytes of nucleofugal genotype conserved a nucleofugal morphology when they migrated out into the iris or cornea of the host, regardless of its genotype, donor melanocytes of nucleopetal genotype assumed shapes which varied all the way from typical nucleopetal to nucleofugal morphology with no correlation between the genotype of the host and the morphology of the donor cells. It therefore appears that although the genes at both the *D* and *Ln* loci exert their activity from within the developing melanoblast, the number and size of dendritic extensions of a melanocyte is also a function of the environment in which the cell occurs. Dilute (*dd*) and leaden (*lnln*) melanocytes have an innately weak capacity for extending dendrites, as reflected in their altered morphology in the rather compact environment in which they normally occur. However, in the less restrictive tissue environment produced by grafting to the eye, these cells do extend more and larger processes and frequently resemble nucleofugal cells. Thus the genotype of the melanocyte, in so far as the *D* and *Ln* loci are concerned, is distinctly expressed only in suitable compact tissue environments.

Further evidence in favor of a direct action of

the *D* locus within the melanoblast is given in the work of Reed (1938). He transplanted skin from newborn albino mice to both non-dilute and dilute newborn hosts. Melanoblasts from the host invaded the transplant and in all cases the *D* locus genotype of the invading cell determined whether dilute or non-dilute pigment was produced.

White Spotting and Albinism

Albino mutants have been recorded in a great variety of mammals (see Little, 1958). The biological basis of albinism is relatively straightforward, but white spotting, though also common to many kinds of mammals, is exceedingly difficult to explain.

Careful histological studies of skin from albino mice (Chase, Rauch and Smith, 1951; Silvers, 1956), rats (Taylor, 1949), rabbits (Cleffmann, 1953) and guinea pigs (Silvers, 1956) have shown that the matrices of the hairs differ from those observed in skin taken from white spotted or piebald areas of these same species (Lubnow, 1939; Taylor, 1949; Chase, Rauch, and Smith, 1951; Meng, 1955; Silvers, 1956; Quevedo and Chase, 1957). Whereas the follicles of white spots are characterized by matrices consisting of regularly arranged cells of equal size, albino hair follicles contain, in addition, many large clear cells in their upper bulb regions. Histological observations suggest that like the clear cells of the superficial epidermis these hyaline cells are amelanotic melanocytes, i.e., melanocytes which are in every respect "normal" except for their inability to synthesize melanin. This interpretation is strengthened by the finding that lightly pigmented genotypes of the mouse exhibit the same type of cell, in exactly the same regions of the matrix, except that pigment granules are demonstrable in the cytoplasm (Silvers, 1956). Further evidence of the synonymity of clear cells and amelanotic melanocytes in the follicle has recently been obtained. Quevedo (1956) demonstrated that the experimentally depigmented melanocytes of black and yellow mice maintained on a biotin-deficient diet closely resembled the clear cells of albinos, though they retained their Dopa-positive character. Quevedo (1957) has also found that a marked destruction of follicular clear cells follows the x-irradiation of the skin of albino mice when the hairs are in the resting stage. This is consistent with the fact that the same dosage of x-irradiation of resting hair follicles of *pigmented* mice results in the almost complete destruction of the follicular melanocytes (Chase, 1949; Chase and Rauch, 1950). The similar radiosensitivity of clear cells and melanocytes, added to the morphological evidence noted above, makes the case for their identity almost unequivocal.

Using the experimental procedure of Rawles (1940, 1947) as previously described, Silvers (1958a) has investigated the embryological origin of the follicular clear cell by transplanting neural crest-free and neural crest-containing tissue from 10 to 13½ day old albino and potentially pigmented embryos to the spleens of adult albino and pigmented F_1 hybrid mice. These experiments have established two facts: first, that the absence of neural crest cells in the transplanted embryonic tissues was associated with the absence of both melanocytes and clear cells in the hair bulbs of the developing grafts and, second, the presence of neural crest cells in the transplanted tissue resulted in the presence of melanocytes in grafts originating from a potentially pigmented genotype and the presence of clear cells in grafts originating from albinos. These findings indicate that clear cells are associated with the presence of the neural crest, and leave their identity as amelanotic melanocytes beyond question.

Whereas albinism appears to stem from a genetically determined biochemical block in melanogenesis in melanocytes which are otherwise present in normal numbers and distribution, the basis of white spotting is still unknown. It is of interest that whereas a single major locus is concerned with albinism (in man there is some evidence that a gene for albinism may also be sex-linked, the males showing the defect, and the transmission being through unaffected mothers—Pearson, Nettleship and Usher, 1913), white spotting is the expression of a multiplicity of loci. This is particularly evident in the mouse, where 13 different loci are believed to be associated with white spotting. Moreover, many of these genes are associated with other effects (i.e., are pleiotropic). For example: (1) *Varitint-waddler* (*Va*), a semi-dominant, which besides producing a curious combination of color dilution and spotting of the fur in the heterozygote is also a behavior mutant (Doel, 1954); (2) *Steel* (*Sl*) and (3) *Dominant spotting* (*W*, W^v, *Wf*) which, in addition to affecting the pigment-forming system, also affects the blood and reproductive systems (Russell, 1954; Bennett, 1956); (4) *Flexed tail* (*f*),

a recessive gene, associated with white belly spotting, ankylosis of the tail vertebrae and a siderocytic anemia (Hunt, Mixter, and Permar, 1933; Kamenoff, 1935; Grüneberg, 1942a, b); *Microphthalmia* (*mi*) and *White* (Mi^{wh}), alleles which affect the eyes and bone absorption in addition to their effects on pigmentation (Müller, 1950, 1951–1952; Bateman, 1954); finally (6) *Splotch* (*Sp*), a semi-dominant which produces ventral spotting. *SpSp* homozygotes are completely inviable and die at approximately 14 days in utero, exhibiting numerous abnormalities including overgrowth of neural tissue and reduction or absence of spinal ganglia (Auerbach, 1954).

Genes, *Sl*, *W*, W^v, W^j, Mi^{wh} and *mi*, when homozygous, produce animals which are completely white. These animals are essentially "one big spot," since their hair follicles do not contain demonstrable clear cells (Silvers, 1956). That there is nothing the matter with their genetic capacity to produce melanin follows from the fact that these genotypes have pigment in their retinas (Markert and Silvers, 1956). It is pertinent that retinal melanocytes originate from the outer wall of the optic cup instead of from the neural crest.

The matrices of hair follicles arising in white spotted areas are indistinguishable from the follicles of white hairs produced by x-irradiation of initially pigmented follicles (Lubnow, 1939; Chase and Rauch, 1950). They are also indistinguishable from hair follicles which develop in skin deprived of neural crest derivatives (Silvers, 1958a). It can be assumed, therefore, that a white spot is due either to the absence of melanoblasts or to their failure to differentiate in that area. The absence of melanoblasts could result from either (1) a neural crest defect—e.g. as might result from a disturbance of the region of the developing embryo which included the neural crest and which, therefore, interfered with the differentiation of its cells, (2) a migratory defect which resulted in melanoblasts not reaching all or some areas of the embryo, or (3) a failure of potentially pigmented cells to survive in the "spotted-environment". Several considerations can be brought to bear in evaluating these possibilities, and it must be recognized that since there are many genes concerned with white spotting it is possible that more than one of the above may be responsible.

A neural crest abnormality as a general cause for all white spotting would have to be specific to the pre-pigment strain of cell, since other derivatives of the neural crest including cranial and spinal ganglia and adrenal medulla are apparently normal, except in the case of *splotch*, where the homozygote (*SpSp*) dies in utero exhibiting abnormalities of other neural crest derivatives (Auerbach, 1954).

White spotting could be the result of a general metabolic disturbance affecting the melanoblast during its migratory phase and consequently preventing its reaching all areas of the epidermis. This etiology for spotting is particularly intriguing in the mutants of the *W*-series, since it has been shown in the exquisite experiments of Mintz and Russell (1957) and Mintz (1957) that in mice homozygous for *W*, W^v or W^j the migration of primordial germ cells from the yolk sac splanchnopleure to the germinal ridges is retarded. Accompanying this retardation of migration there is a general mitotic insufficiency of primordial germ cells. It is of special interest here that the migration of these primordial germ cells takes place during the same embryonic period, 8–12 days, when primordial pigment cells are migrating to their definitive positions from the neural crest.

A failure of melanoblasts to survive in a white spot would have to involve a definite critical period, in so far as development is concerned, since melanoblasts survive and differentiate in hair follicles of skin from potentially spotted regions when transplants are made to potentially pigmented areas shortly after birth (Rawles, 1955; Silvers and Russell, 1955). Melanocytes also persist and produce pigment when they become established in hair follicles arising in white spotted areas of adults (Pepper, 1956; Silvers, 1958d). This critical period, therefore, would have to occur very soon after the melanoblast's arrival from the neural crest. It is also possible that melanoblast differentiation involves a sequence of steps and that the tissue environment —the skin—of the white spot does not present an adequate stimulus for one of these steps to take place so that melanoblast differentiation is arrested. Melanoblasts which migrate into white spotted areas after reaching a more advanced stage of differentiation would, however, be expected to mature completely and elaborate melanin as in the transplantation studies noted above.

A failure to sustain melanoblast survival or

differentiation might characterize the tissue in which the spotting occurs, or, alternatively spotting might be accounted for by assuming a primary effect within the melanoblasts themselves. It is hard to believe that this latter hypothesis could account for the complex and regular striped pattern of the zebra. It would be expected that any mechanism operating within the melanoblast that reduced the population which differentiated or survived would almost certainly result in a dilution effect rather than a spot. The mutant *silver* (*sisi*) may indeed involve such a mechanism. This mutant exhibits an intermingling of white, black and mosaic hairs (Dunn and Thigpen, 1930). Moreover, a phenocopy of this mutant is produced following the destruction of melanocytes with x-irradiation (Chase, 1951). A similar situation is found in the silvering process in the Champagne d'Argent rabbit (Quevedo and Chase, 1957). Support for the hypothesis that a genetically determined destruction of melanoblasts is responsible for white mottling is presented by the plumage of White Leghorn chickens (Hamilton, 1940). Here melanoblasts differentiate in the feather follicles but die before depositing noticeable quantities of melanin.

Since melanoblasts throughout the body are genetically alike, the responsibility for white spotting might best be explained in terms of an environmental effect on the melanoblasts which occur in the spotted area. If such is the case, one would expect to obtain functional melanocytes from animals destined to be "one big spot" by experimental procedures permitting the migration of melanoblasts from these genotypes into an environment expected to promote the differentiation and functioning of these cells. Markert and Silvers (unpublished) have transplanted various tissues presumed to contain neural crest derivatives from both potentially pigmented and potentially black-eyed white embryos, ranging from 9 to 16 days of age, to the anterior chamber of the eye of albino hosts. No pigment was formed in transplants originating from black-eyed white embryos. However, since most of a large number of explants originating from potentially pigmented genotypes also failed to produce pigment, these findings contribute little toward solving the problem. It seems certain that all these grafts initially contained melanoblasts, and therefore the basis for the failure of melanoblast differentiation to occur (see Markert and Silvers, 1959) presents an additional problem.

In the guinea pig white spotting depends primarily on a recessive factor, *s*, with many minor genetic factors having additive effects (Wright and Chase, 1936). It is of interest that even in highly inbred strains of white-spotted guinea pigs there is a tremendous amount of variation in the relative amounts of non-pigmented and pigmented areas. Wright's (1926) extensive investigation revealed that the mother's age was a major determinant factor, the amount of white spotting increasing with age of the dam (see also Foster, 1954).

Although congenital white spotting in man has a genetic basis (Macklin, 1948) and appears to be polygenic, it has yet to be established whether spotted areas lack melanocytes. It seems apparent from the evidence presented for other mammals that the basis for such white spotting is probably similar to that of rodents. The term *partial albinism*, which has been used for white spotting in man, should now be recognized as misleading and be removed from the literature, since Barnicot, Birbeck, and Cuckow (1955) have shown that albinotic hair follicles contain amelanotic melanocytes. Partial albinism seems more appropriate to describe the condition of the Himalayan rabbit, and certain other mammals of similar phenotype, whose melanocytes may be melanogenic or apparently amelanogenic according to environmental conditions. Although predominantly white, the fur of this animal is normally pigmented at the extremities. However, pigmented hair can be caused to appear in other regions of the body simply by shaving the skin and maintaining the animals in a cold environment (Schultz, 1920). This leaves no doubt as to the presence of potentially functional melanocytes in the white areas of these animals.

Considering melanocytes in mammals as unicellular, pigment-secreting cytocrine glands, the genetic determination of their disposition and functional activity may appear to the uninitiated to be exceedingly complex. In comparison, the genetics of human blood group substances is relatively simple and straightforward, since each is usually determined by a single genetic locus and the antigen produced is almost a direct reflection of the primary gene product. With pigmentation, by contrast, the final formation of the granule almost certainly involves a series of geneti-

cally controlled steps, any one of which can be affected in various ways. It therefore presents a much more dynamic system for analysis, a fact which accounts for the great interest of mammalian geneticists in pigment. Indeed, a systematic analysis of mammalian pigmentation probably offers the best opportunity for determining how gene action and interaction can influence the nature and deployment of the final product of a single cell.

Melanocytes and Pigmentation Patterns in Birds

Results similar to those described above for mice had previously been obtained in experimental analyses of avian pigmentation patterns, employing tissue transplantation techniques (see review by Rawles, 1948). As in the mouse, the kind of melanin deposited and the patterns produced are the result of two independent but interacting factors: (1) the genotype of the melanoblast and (2) the tract specificity, i.e., the epidermal substratum of the feather germ in which the melanocyte elaborates pigment. Superimposed upon these two facts, hormones have been shown to play a predominant role in conditioning the follicular environment at least in certain birds including the domestic chicken, so that the kind of melanin produced is due to complex interactions of melanoblasts with both tissue and humoral factors. In general, the feather germ furnishes certain physiological conditions which in turn act upon the melanocyte. The responses of the melanocyte to these different physiological conditions are dependent upon its genetic constitution.

The importance of the genetic constitution of the melanoblast in determining both the nature and patterns of melanogenesis has been illustrated in a number of studies. Willier and Rawles (1944) transplanted melanoblasts from female and male hybrid embryos (Rhode Island Red × Barred Plymouth Rock) to White Leghorn embryos. In every case they found that the sex genotype of the transplanted melanoblasts determined the type of pattern produced, whereas the sex genotype of the feather germs, in which the melanocytes expressed themselves, had no effect on the final pattern produced. However, the *specific* pattern produced by either male or female melanocytes depended upon the tract origin of the overlying epidermis. For example, as shown by Wang (1943), a saddle feather papilla, from which the epidermal cells have been removed, produces a breast feather when transplanted to an empty breast follicle, whereas intact breast or saddle papillae retain their specificity in follicles of either tract. The physiological properties of the individual feather germs, such as tract location and their growth rate, act as modifying factors which affect the melanoblasts, resulting in variations in pigment patterns for different regions of the bird. This is further exemplified by the results of transplantation studies between New Hampshire Red and Barred Rock or White Leghorns (Rawles, 1944). When New Hampshire Red melanoblasts migrate into feather germs of Barred Rock or White Leghorn origin, both the kind of melanin elaborated and the pattern produced is the same as for corresponding regions of the donor breed—i.e., the melanocytes retain their donor specific characteristics in these respects. Thus, in the saddle feather of the hosts, the solid red uniform pattern characteristic of the normal New Hampshire Red saddle feathers is produced and in the wing feathers the red and black splotched pattern develops which normally would be found in homologous New Hampshire Red feathers. Here is a situation closely resembling that which occurs in mice, where certain regions of black animals (e.g., ear, gonad, mammae) are characterized by yellow pigment-containing hairs (Silvers, 1958b). In these cases the local milieu in which the melanoblast differentiates (i.e., the epidermal substratum of the particular feather or hair germ) determines whether a melanocyte will produce melanin of the xanthic or eumelanotic type. The nature of the *specific* factors which determine the kind of pigment a melanocyte will produce is still unknown.

While hormones are known to have some effects on mammalian pigmentation (see below) they certainly exert a dominating influence on melanogenesis in certain breeds of chickens (see Willier, 1942, 1948). The influence of thyroid and estrogenic hormones on the pigment pattern in the Brown Leghorn has been beautifully demonstrated in a number of studies by Trinkhaus (1948, 1950, 1953). He has shown that although the Brown Leghorn melanocyte has the genetic capacity to respond to both thyroid and estrogenic hormone, this capacity can only be expressed in a structurally organized and mature feather germ. When Brown Leghorn melano-

blasts differentiate in vitro, or are introduced into an immature epidermis, they fail to respond to hormonal treatment. Hormones evidently can only condition the follicular environment of *mature* feather follicles, which in turn affect the expression of the melanocyte.

XII. THE PHENOMENON OF PIGMENT SPREAD

Of all the aspects of the biology of the mammalian melanocyte none is more intriguing or more challenging than the phenomenon of pigment spread, first described by Carnot and Deflandre (1896) and independently confirmed by Leo Loeb (1897). If black skin from a black and white spotted guinea pig is grafted to a white area on the same animal there is a slow centrifugal encroachment of pigmentation into the white skin from the graft margins (Fig. 7). Conversely, if white skin is grafted into a black area it blackens from its periphery inwards. Subsequent studies have shown that this phenomenon is not restricted to guinea pigs, and that it also occurs naturally; grafting simply affords a convenient mean of expediting and bringing it under experimental control.

At birth in a patched or spotted guinea pig the areas of black skin bearing black hairs are incisively distinct from areas of white skin bearing white hairs, or from red skin bearing red hairs. As the animals grow up there is a slow "spread" of pigmentation from the black into contiguous white or red areas or from red into white areas, so that in the adult there are "transitional" zones between the patches, up to 1 cm in width, in which the color of the superficial epidermis has been altered but the hairs have retained their original coloration. The phenomenon takes place much more rapidly at the margins between black and white or between red and white areas, than between black and red areas. Among the various piebald animals, some of which belong to widely different groups of mammals, in which this phenomenon takes place are cattle (Anderson, Billingham, Lampkin, and Medawar, 1951); pigs, dalmation dogs, sheep (Hardy, Frazer, and Short, 1952) and mice, in which it is restricted to the skin of the tail (Reynolds, 1954). There is even a rare case of recessive spotting in man in which pigment spread apparently occurred (Pearson, 1913).

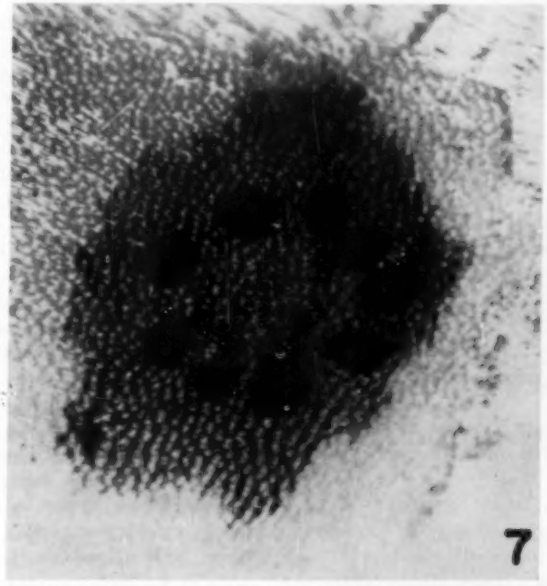


FIG. 7. THE "SPREAD" OF PIGMENTATION FROM 9 SMALL BLACK EAR SKIN GRAFTS TRANSPLANTED TO A WHITE SKIN AREA ON THE TRUNK OF A SPOTTED BLACK AND WHITE GUINEA PIG

These grafts are of more than 150 days standing. Annuli of spread from the individual grafts have coalesced. The hair color has been unaffected by this radial spread of pigmentation from the grafts. × 2

Although this phenomenon has been investigated repeatedly (Sale, 1913; Seelig, 1913; Seevers and Spencer, 1932; Saxton, Schmeckebier and Kelley, 1936; Lewin and Peck, 1941; Kelley and Loeb, 1939; Fessler, 1941; Lewin and Peck, 1941; Loeb, 1945; Barker, 1947; Billingham and Medawar, 1948a, 1950b) no completely satisfactory or generally acceptable explanation of the underlying mechanism has yet been forthcoming.

Since melanogenesis is the sole prerogative of melanocytes in skin, some workers (Rawles, 1948, 1955; Meng, 1955) maintain that pigment spread is brought about by a differential migration of melanocytes or melanoblasts from black or red skin into white, or from black skin into red skin. In development it is certainly true that melanoblasts do migrate from their presumptive position in the neural crest to their definitive position in the skin, as Rawles' (1940, 1947) elegant analysis has shown. Zimmerman and Becker (1959), using an ammoniated silver nitrate technique, have made a special study of these pigmentary precursor cells in fetal Negro skin and have emphasized how propitious the early fetal dermis is for movements of these cells. The present hypothesis assumes either that melanocytes retain their migratory ability even into adult life, or alternatively, that in adult skin, besides the differentiated melanocytes, melanoblasts are also present which are responsible for pigment spread.

The most recent hypothesis, put forward by Billingham and Medawar (1948a, 1950b), attributes pigment spread to the serial propagation from cell to cell of an infective and inherited transformation of white (or red) into black (or red) melanocytes. Where skin regions of different color—for example black and red—are juxtaposed, either naturally or as a consequence of grafting, it is argued that red and black melanocytes may establish protoplasmic connections between one another through fusion of their branches, or through termination of an end-button of the one cell on the perikaryon of another. In this way, through their normal cytocrine activity, cytoplasmic ingredients from a black melanocyte may gain access to a nearby red melanocyte and permanently transform its pigmentary system so that it now elaborates the pigment characteristic of the black melanocyte. Once transformed, a red melanocyte would then be capable of transforming another in a similar manner and so on, so that the spread of pigment is analogous to an infection. An essentially similar explanation has been put forward to account for pigment spread in newts where "infection" is believed to occur as a result of the ingestion by melanophages of cytoplasmic matter from the melanocytes (Niu and Twitty, 1950).

So far as the spread of pigmentation from black into red skin is concerned Billingham and Medawar's experimental evidence in support of their hypothesis is essentially as follows: Careful studies on whole mount preparations of the epidermis from pale red ear skin grafts which, following their transplantation to black skin areas, had been partially encroached upon by black pigmentation, revealed that (1) the originally weak-red colored melanocytes from those parts of the grafts which had been encroached upon by black pigment were now fully black, and completely indistinguishable from those present in the black skin elsewhere on the body, and there were no red melanocytes present in these encroached-upon areas of the grafts; (2) in those parts of the grafts which had not yet undergone a transformation of color, only red-colored melanocytes could be found; (3) nowhere were both black and red melanocytes intermixed as one would expect according to the migration hypothesis. However, on the basis of a more recent histological analysis of the natural encroachment of black pigment into a red skin area, Meng (1955) has claimed that through migration an intermingling of red and black melanocytes does take place, the black areas spreading more rapidly than the red ones.

Pigment spread takes place most rapidly and spectacularly from black skin into white, and for this reason it has been the color combination most widely employed in attempts to analyse the phenomenon. Billingham and Medawar (1948a, 1950b, 1953) have presented a considerable amount of experimental evidence based on the use of this color combination, too lengthy to be summarized here, that they feel is inconsistent with the melanoctye migration hypothesis. The great weakness in the infection theory of pigment spread is that amelanotic melanocytes have never been demonstrated directly in the basal layer of the epidermis or in the hair matrices in white skin areas of spotted guinea pigs. At present their existence has to be *inferred* from the consistent presence of what have been inter-

preted as their effete end-products in the higher epidermal strata as revealed by gold impregnation or staining with quinone imine dyes such as methylene blue (see Section VIII). Unfortunately, neither of these "stains" is specific for melanocytes (Fan and Hunter, 1958) or their derivatives and, at least in the opinion of some workers, there are grounds for suspecting that the network of dendritic cells revealed by these stains may bear no relation to melanocytes (see Ferreira-Marques, 1951; Rawles, 1955; Silvers, 1957b). As discussed previously, there is some basis for believing that white spotted areas lack melanocytes completely, and the observation that pigment spread occurs more rapidly from black into white areas than from black into red areas might be attributed to this fact.

The finding by Billingham and Medawar (1950b) that, contrary to expectation from the laws of transplantation immunity, pigment spread could be initiated and the pigmentation long maintained thereafter, in the skins of spotted guinea pigs by means of "cellular" homografts of dissociated epidermal cells including melanocytes, prepared from black skin of an unrelated guinea pig, opened up a new approach to the problem. So far as it goes, the immunological evidence obtained favors the infection hypothesis over that of migration. Immunogenetic experiments of Billingham and Silvers currently in progress on two inbred strains of spotted guinea pigs should at least enable them to establish whether the melanocytes in the annulus of pigment spread around a black-in-white graft are of graft origin or not—a crucial point for the migration hypothesis.

The phenomenon of pigment spread still presents a challenging problem. What determines the asymptotic decline in the rate of spread following grafting has still to be elucidated. Fábián's (1953) observation that the spread in denervated guinea pig skin is more extensive than in normal skin may be pertinent here. If the infection hypothesis finally prevails, its implications for biology in general need hardly be stressed: it would imply that differences between the various melanocytes of a single individual are due to cytoplasmic differences. Furthermore, it would represent the first example of an autonomous cytoplasmic component that gives cytoplasmic inheritance in a mammal at the somatic cell level.

XIII. ENDOCRINOLOGICAL CONTROL OF MELANOCYTE ACTIVITY

It is well known that certain physiological changes or pathological conditions involving hyper- or hypofunctioning of endocrine glands are accompanied by an increase in melanin formation. Familiar examples are Addison's disease, acromegaly, the darkening of the perianal skin and the areola of the nipples with the approach of puberty, the intensification of the areolar pigmentation, and the not infrequent occurrence of pigmented patches on the face during pregnancy. Extensive studies have been made on the relationship between various hormonal factors and melanin pigmentation in mammals. While it is beyond the scope of this review to deal at length with these (see Bissonette and Bailey, 1944; Lerner, Shizume, Fitzpatrick, and Mason, 1954; Lorincz, 1954; Fitzpatrick and Lerner, 1954; Wolff, 1954; Lerner and Takahashi, 1956; Levin, 1956; Quevedo and Smith, 1958; Bischitz and Snell; 1958a, b; Lerner and Case, 1959), a review on mammalian pigmentation would not be complete without some mention of the major endocrinological factors which affect the elaboration of melanin.

The most important hormone(s) affecting pigmentation appears to originate in the intermediate or anterior lobe, or both, of the pituitary and has been known as intermedin, melanophore hormone, melanophore dilating principle, and melanocyte stimulating hormone (MSH). The last mentioned name seems most appropriate. Melanocyte stimulating hormones have, during the past few years, been isolated from both hog and beef pituitary glands (Lee and Lerner, 1959), and have been observed to darken the skin when injected into man (Lerner and Case, 1959). It is now possible to explain the hyperpigmentation associated with adrenal insufficiency, as in Addison's disease; the lack of adrenocortical hormones which normally inhibit the release of MSH from the pituitary gland results in increased MSH secretion and therefore increased melanocyte stimulation (Lerner, Shizume, and Fitzpatrick, 1953).

Other hormones, such as noradrenaline, adrenaline, hydrocortisone, progesterone, estrogens, androgens and thyroid hormones have all been cited as having some effects on pigmentation (see Lorincz, 1954; Levin, 1956). These hormones either directly affect the melanocyte

or, as in certain clinical conditions, produce their effects indirectly through the pituitary, as in Addison's disease. It is also likely that at least some of these hormones may produce their effects on melanogenesis by conditioning the epidermis. This seems reasonable since the elaboration of melanin by a melanocyte is known to be influenced by changes in its local milieu.

One of the most striking phenomena associated with mammalian pigmentation is the adaptive seasonal change in coat color in certain arctic species such as hares, stoats and foxes (Cott, 1940). These changes are the outcome of molting of the hairs of one color and their replacement by the regrowth of hairs of the new color in a definite temporal sequence which varies in different regions of the body and in different species. Careful experimental studies in weasels have shown that these molts and associated color changes can be terminated or drastically altered by manipulation of light cycles (Bissonnette and Bailey, 1944), and it is the consensus that altered daily periods of illumination is the predominant factor which induces these changes (Bissonette, 1935; Bissonette and Wilson, 1939; Lyman, 1942). Other factors may operate indirectly by altering the period during which the animals expose themselves to light. This light stimulus is almost certainly received through the eyes and acts via the anterior lobe of the pituitary gland, since hypophysectomy abolishes the cyclic molting and regrowth of hair in ferrets (Bissonette, 1935). Lyman's (1942) demonstration that castrated and thyroidectomized varying hares continue to undergo cyclic color changes suggests that neither thyroid nor gonadal hormones are involved.

Unfortunately, so far as we are aware, the fate or role of the melanocytes in these seasonal changes has never been investigated.

XIV. ADDITIONAL REMARKS

In nearly all mammals, and in most other vertebrates too, melanocytes have two important functions: they increase the optical efficiency of the eye, and they are responsible for the production of color patterns, usually of adaptive significance, in the hairs and/or the superficial epidermis.

The characteristic nuclear-capping distribution of melanin granules observed in Malpighian cells of the superficial epidermis is commonly interpreted as having protective significance with respect to solar radiation, particularly in man with his relatively hairless skin. There is, however, little evidence to support this view and indirect evidence which is difficult to reconcile with it: for example, the fact that this distribution of pigment granules is seen in very young animals, in epidermal cells covered by thick hair coats, in the Malpighian cells of the smooth hairless skins of whales, and in the epithelium of some of the mucous membranes of man. So far as man is concerned there is no convincing evidence that Caucasians with their acquired feeble sun-tan are any less well able to withstand prolonged exposure to sunlight in tropical conditions than Negroes with their innate deep pigmentation. The thickened stratum corneum seems to afford an efficient filter against ultraviolet light (Blum, 1945; Barnicot, 1957).

Since the epidermis is of dual origin and almost invariably of composite structure, including in its make-up both Malpighian cells and melanocytes, many authorities have felt that the latter may fulfill some important function other than, or in addition to, melanogenesis. Masson (1948a) considers that melanocytes act as intermediaries in exchanges of materials between a postulated symplastic network formed by dermal fibroblasts and the Malpighian cells (the synonym "cellules amboceptrices" reflects this view). It must be pointed out however, that even the infrequent occurrence of anastomoses between processes of fibroblasts and of melanocytes respectively is dubious, and the experimental evidence cited in support of this view is derived from pathological conditions (Pautrier, Lévy and Diss, 1928).

Billingham and Medawar's (1950a) suggestion that melanocytes form an epidermal glial system implies that they play a mechanical or supportive role. In man, where the presence of a thick epidermis appears to be important in the absence of a dense hair-coat, melanocytes obviously contribute to the general mass of this tissue. Whether the presence of these branching cells is structurally advantageous has yet to be established.

Pinkus, Staricco, Kropp and Fan (1959) have recently attached great significance to the fact that melanocytes and Malpighian cells live in close association and biologic balance, acting together to produce the specific properties of the individual epidermis.

If melanocytes do have functions other than pigmentary activity, probably none is indispensable, as Medawar (1953) has argued. Epidermal epithelia which lack melanocytes have already been cited; moreover epithelia which normally possess melanocytes may be deprived of them by subjecting skin to treatments such as intense local cooling which are relatively harmless to Malpighian cells (Taylor, 1949; Billingham and Medawar, 1952), or by preventing their migration from the neural crest (Rawles, 1947). Epithelia without these cells appear to be under no disadvantage apart from their lack of pigment.

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MICROBIAL GENETICS IN THE USSR

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ABSTRACT

A comprehensive review of Soviet microbial genetics during the period 1940–1958, but especially for the years 1950 through 1957, has been based on 297 translated abstracts and 284 full articles. One full paper and 57 abstracts in this total came from the scientific literature of the People's Democracies; the remainder were from the USSR. In addition, 456 titles or brief indicative abstracts were examined.

The items covered were grouped into twelve major areas of subject matter, in some of which there was evidence of extensive work, in others of very little. The retarding influence of Lysenko and his group upon the development of genetics, and the almost equally restrictive influence of Lepeshinskaya's doctrine of the origin of cells from non-living matter, were widely evident. Work on Mutation, Adaptation, and Variation was scanty and inferior; but in the area of the Chemistry of Inheritance increased activity and interest are apparent. Drug Resistance and Antibiosis, because of practical outcomes, was an emphasized area; genetic methods are being used to screen for antibiotics. Sexual Recombination was a neglected area. Work on Growth, Cell Division, and Cell Theory was strongly under the influence of the Lepeshinskaya school, but there were signs of sharp criticism of those views and an awakening interest in studies like those conducted in the West. Evolution and Ecology was an area dominated by the pro- and anti-Lysenkoist controversy. The effects of altered environments were widely studied; but the role of natural selection as a major factor was mentioned more frequently after 1954. Most papers on microbial Metabolism and Physiology had little orientation toward genetics, but there was some evidence of awakening interest in DNA, adaptive enzyme mechanisms, pure culture techniques, etc. Host-Parasite Relationships, Medical Microbiology, and Immunology make up an area that showed from 1955–56 on an increasing independence of Lysenko and Lepeshinskaya, as discussion, if not laboratory experimentation, focused on bacteriophage studies, the biochemistry of phage infection, and studies of plant and animal viruses. Some of the work in the field of Industrial Microbiology and Methodology also showed, after the mid-fifties, a departure from Michurin-Lysenko doctrine, and even inter- and intra-specific competition was thought to be involved in the production of useful varieties. On the whole the trends in the industrial laboratories closely reflected the progress and ideas in the microbiological laboratories devoted to basic research. Radiation Biology was a field in which the workers seemed thoroughly acquainted with the Western literature on the subject and were using a wide variety of up-to-date methods. In the category of Miscellaneous and General Microbiology the use of ultrasonic methods and great interest in soil microbiology were notable. Finally, History and Ideology represent an important element of the genetic microbiological picture, for reasons already given. The major trend was a decline from the mid-fifties of the once complete dominance of Lysenko and Lepeshinskaya. A more critical, better informed science is developing. A major defect in the scientific literature of USSR microbial genetics has been the characteristic tendency of workers to discuss in general terms and draw sweeping conclusions without supplying either a sufficient account of the experimental methods they used or their quantitative data. Again, a trend toward a more critical, adequately documented presentation of scientific findings is apparent since the mid-fifties. Rapid progress is now being made in this field, and Soviet workers seem to be fully aware of the latest advances in microbial genetics which have been made elsewhere in recent years.

INTRODUCTION

THE progress of microbial genetic research during the past decade has greatly influenced genetic concepts throughout much of the world. The methods employed in microbial genetic studies, as well as many of the results obtained, have contributed directly toward an increased understanding of numerous medical, epidemiological, agricultural, and industrial problems. The rapid development of tissue culture research owes a great deal to the use of techniques originally introduced in the field of microbial genetics.

While microbial genetic research publications of the United States, Western Europe, and parts of Asia have been generally available in this country through journals, reviews, monographs, and other publications, relatively little information has been available to indicate the progress of microbial genetic research in the USSR and the "People's Democracies." The purpose of the present review is to evaluate as much as possible of the work now being done in microbial genetics in that part of the world, and to point out whatever trends are discernible in the investigations carried out by Russian and allied investigators.

The material covered in this report has been arbitrarily divided into a number of subjects, or research areas, which together represent a cross-section of the available Soviet microbiological literature relating to microbial genetics. While there are undoubtedly overlaps between the subdivisions, it was felt that such subdivision would simplify presentation. Consequently all of the material reviewed has been subdivided as follows:

1. Mutation, Adaptation, and Variation
2. Chemistry of Inheritance
3. Drug Resistance and Antibiosis
4. Sexual Recombination
5. Growth, Cell Division, and Cell Theory
6. Evolution and Ecology
7. Metabolism and Physiology
8. Host-Parasite Relationships, Medical Microbiology, and Immunology
9. Industrial Aspects and Methodology
10. Radiation Biology
11. Miscellaneous—General Microbiology
12. History and Ideology

While this report deals with research from about 1940 to 1957, most of the available material was published between 1950 and 1957.

This review emphasizes several points in each research area. A summary of the major findings of numerous Soviet scientists is presented, and the techniques used as well as the nature and worth of the experimental data are considered. The extent of familiarity with contemporary U.S. and Western research in the area is noted, and finally, an evaluation of the quality, scope, and direction of the research is attempted.

Following the discussion of the individual research areas, the overall pattern of Soviet microbial genetic work will be reviewed in an attempt to estimate the current trend of research and to compare it with Western investigations, and some effort will be made to estimate the research potential in this field. The status of work in the "People's Democracies" will be discussed briefly and compared with that in the USSR and the West.

In an appendix, a summary is presented of the subject matter and publication date of the source material included in this review. The evaluation is unfortunately limited, since no attempt has been made to prepare an exhaustive bibliography of all relevant published material. From the materials that were available in translated form, only those items have been included that seemed pertinent to a particular part of the review.

This review of USSR research in microbial genetics is based on the screening of a large number of references. About one-third of this material was available in the form of fully translated discussion and experimental papers, another third in the form of translated abstracts, and the remainder was available only by title or in the form of very brief abstracts which provided little information as to content.

The fully translated papers span the period from about 1940 to 1958, but most of them fall between 1950 and 1957.

1. MUTATION, ADAPTATION, AND VARIATION

Alikhanian (1956–1957) presented work on the "heterosis" of different strains of *Penicillium* which led to increased penicillin production. He claimed that this heterosis, which probably resulted from the formation of heterocaryons, occurred between different species as well. Studies were reported on the effects of x-rays on the production of albomycin by actinomycetes, with the subsequent selection of variants which produced 500 to 600 times the level of albomycin normally found in unselected strains. He reported on the combined mutagenic and lethal effects of ultraviolet irradiation and

ethyleneamine on actinomycetes, and on the use of biochemical mutants of actinomycetes to select hybrids. It appeared that some of the methods used by Western scientists for mutant isolation, as well as the use of biochemical genetic markers, were familiar to the workers in this group. The work indicated some understanding of the problems of cross-feeding and heterocaryosis, and contact with Western literature up to 1954. Alikhanian still considered it unlikely that bacterial and fungal hybrids occurred by a sexual process akin to that found in higher organisms. Generally speaking, the methods, data, and literature citations in this particular research work were better than the average Soviet paper in this area.

There were many accounts of "controlled mutation" in microorganisms, i.e., of directed mutation. One example was found in the work of Ayrapetyan (1954) on controlled mutation in the *Pasteurella* group through "vegetative hybridization." The work supposedly showed that when *P. bovisepticum* was cultured on breakdown products of *Escherichia coli*, there were hereditary changes in its biochemical properties, virulence, and antigenicity. This effect was also claimed when *E. coli* was treated with *P. bovisepticum* products. Reference was also made to the many instances of interspecies conversion by similar methods, as carried out by Gracheva, Timakov, Kalina, and others. In this paper and in numerous other papers in the same general area of "directed modification" research, the methods and the data were wholly inadequate. No grounds for the claims made were evident in the published material. Often the methods were ill-defined. For example, in one paper on interconversions involving *Rhizobia* and "tubercle bacilli," two to ten months of incubation were required; in other cases as many as sixty passages were involved, the transfers being made at weekly intervals. In these experiments there were inadequate controls for contamination and other sources of error. For the most part, the references were to USSR papers, although occasionally (Krasilnikov, 1955) there were citations to Western work on transformation, transduction, and recombination. Undoubtedly, some later effort was made to equate these "controlled modification" experiments with Western microbial work on transformation and similar phenomena.

It is noteworthy that in this work on "directed modifications" such technics as replica plating, gradient plating, the proper use of biochemical markers, drug, antibiotic, or colicin resistance, or phage resistance, and quantitative growth measurements were not employed perhaps because they were unknown. There was undoubtedly great political and ideological pressure in this field, for the success of such work was taken as direct experimental proof of Michurin-biology and Lysenkoism, i.e., as proof of the value of USSR materialistic over Western idealistic scientific concepts.

The same conclusions applied to the studies of many USSR workers on "filterable forms of bacteria." A paper by Goldin (1953–1954) on the "non-cellular forms of life" may serve as example. No data were presented which could support the contention of the USSR scientists that microbial life, as well as that of higher organisms, arises from "non-cellular living material." It was evident that the influence of O. B. Lepeshinskaya's work (nonmicrobial), and its approval on political-ideological grounds, had apparently influenced this entire biological area. Her concept led in this instance to the proposal that "filterable forms of bacteria" were developmental stages in the life cycle of the bacterial cell. There appeared to be some disagreement among the USSR scientists, however, as to whether "filterable forms" were breakdown products or developmental stages. There was no indication that the Soviet scientists engaged in this work were familiar with Western studies on the formation of protoplasts by means of penicillin, lysozyme, EDTA, and other agents, and since the "filterable forms" referred to were sometimes prepared by treatment with penicillin, it may be that they were really protoplasts. (According to the USSR literature, treatment of bacteria with agents ranging from ultrasonics to drugs and antiserum can bring about the formation of "filterable forms.") Most difficult to resolve were the claims, unsupported by adequate experimental details or data, that new species of microorganisms can be generated from these "filterable forms." It was emphasized that the idea of "directed mutation," as well as the "regeneration of new types of bacteria from filterable forms," agreed perfectly with the Michurin-Lysenko doctrines, that is to say, that a change in living conditions will cause a change in metabolism and subsequently a directed change in heredity. Such changes were not explained by the occurrence of spontaneous random mutations followed by selection, or by a temporary nonheritable change due to environment. The view adopted emphasized, strictly speaking, the inheritance of acquired characters. While recent Western studies on "gene conversion," the "copy-choice" mecha-

nism of DNA replication, and the specific chromosomal effects of certain chemical mutagens raise questions regarding the existence of specific genetic-environmental interactions, no data in the USSR papers provided significant information on this subject.

Some interesting work was reported by Gauze (1956–1958), who covered several subjects, including a study of variants of actinomyces with different albomycin-synthesizing capacity, and the use of respiratory-deficient mutants of *E. coli* and *Staphylococcus aureus* in order to screen for antibiotics active against cells with high glycolytic activity and low aerobic metabolism. Gauze suggested that microbial mutant cells which are respiratory-deficient, i.e., are less sensitive to cyanide and exhibit a loss of the cytochrome b_1 band, may be sufficiently similar to cancer cells to use as screening organisms for anti-cancer agents. The methods employed by his group appear reasonable and the data were supplied. Gauze seemed to be familiar with the Western literature on the cytochromes, yet oddly made no reference to Ephrussi's work on respiratory-deficient yeast or to Mitchell's work on a respiratory mutant of *Neurospora*. By and large, the work from Gauze's group seemed interesting and relatively free from ideological pressure.

It might be of value to indicate some of the research subjects investigated by USSR scientists in the general area of Mutation, Adaptation and Variation. These included studies on antigenic changes in foot and mouth disease virus; adaptation vs. mutation in bacteria; directed changes in bacteria, particularly pathogens, resulting in an alteration of species, and the attending medical and epidemiological implications; use of immunological methods to study typhoid variants isolated from water; morphological mutants of *Bacillus mesentericus*; variations in immunological, fermentative, and colonial characteristics in streptomycin and syntomycin-resistant cultures of *Alkaligenes faecalis*, etc.; variation of *E. coli* under the influence of chlorine; distant hybridization of *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*; modification of viruses by animal passage; bacterial mutations; variation studies on single cell isolates of alpha- and beta-hemolytic streptococci; preparation (by culturing a "proactinomycete" with tubercle bacilli) of a tuberculosis vaccine which afforded some protection to guinea pigs (that is, a non-pathogen was converted into a strain having antigenic properties similar to those of tubercle bacilli); the importance of microbial variation to epidemiological and clinical aspects of infectious disease; directed variation of actinophages; and the influence of forced assimilation of proteins and nucleic acids of *Bacillus breslau* on the variability of *E. coli*. This last piece of work seemed to be an attempt at transformation. However, Vizir (1955) prepared his material by "sterilizing" for four days with autoclave, ethanol, and acetone. It was concluded that "evidently the preparations were actually converted into their vegetative cells and into filterable forms of the initial cultures." It took from three to fifty-six passages every three days to bring about a "change in morphology, fermentation, virulence, and immunogenicity."

For the most part, the reports of the aforementioned work shared two points in common. First, the experimental methods were inadequately described. It would be virtually impossible to duplicate any one of these experiments on the basis of the published information. Second, the quality and quantity of data provided in the papers was substandard. Most of the claims made by the Soviet authors working in this field were unsubstantiated in their own publications.

It seems that by 1954 much of the Western literature in the field of microbial genetics had become available to the Soviet investigators, since the literature cited in the later USSR papers included many Western references. One noteworthy publication, a book by Kunicki-Goldfinger (1954), presented a thorough discussion of both the Western literature in this field and the USSR work in microbial genetics, biochemical genetics and allied areas. Of the 784 references about one-half were Western. While there were differences of opinion on the importance of spontaneous mutation vs. directed variation by environment, on certain aspects of gene-enzyme relationships, etc., it appeared that contemporary Western work was being seriously considered in many circles. This publication discussed sex in bacteria, induced enzyme formation, biochemical genetics and nutritional mutants, transformation, transduction, and similar topics. It was evident that Kunicki-Goldfinger was anxious to relate phenomena such as "para-immunity," described by Zilber and others, to transformation, although he candidly remarked that in the Russian studies there were "frequently fragmentary descriptions," and that more work by Soviet scientists was needed in the area.

Some of the work during the period 1954–1958, available only in abstract form, was nevertheless of interest. Emphasis was placed on the use of

pathogens in many experiments on drug resistance and directed modification, for example, the modification of *Brucella* Vi antigen to W by *Brucella* phage; the directed mutation of virulent plague bacilli to avirulent by using the "methods of directed variation" over a four to eleven month daily transfer period; the uptake of P^{32} decomposition products of *Salmonella* by *E. coli*; alterations in the biological and immunological properties of *Salmonella*, *Shigella*, and *E. coli* by streptomycin; and directed antigenic modification of different gram-positive and gram-negative cocci and bacilli by filtrates of tularemia bacteria.

2. CHEMISTRY OF INHERITANCE

Papers on this subject dealt with problems such as the following: the physical and chemical basis of inheritance; the role of nucleic acids in biological-structural-formation processes; changes in the microbial characters induced by transforming substances; processes of renewal and change of nucleic acids in the organism; biochemical genetic work on the relationship between vitamin B_{12} and methionine; problems on the material nature of heredity; the role of nucleic acids in the variability of microorganisms; and the composition of nucleic acids in the experimental mutability of bacteria of the coli group.

Abstracts covering the year 1956 indicated a strong interest in the USSR in problems related to nucleic acid and protein biochemistry, comparative and evolutionary biochemistry, virus reconstitution (combination in vitro of non-infectious solutions of polyhedral virus nucleic acid and protein leading to reconstitution of the virus), nucleic acid and chromosome cytochemistry, and the relation between DNA content and morphogenesis. In the early 1950's, there was an effort to relate the microbial work on nucleic acids and proteins to Lepeshinskaya's concept of "the formation of cells from non-cellular living matter." During this period the emphasis was on protein synthesis, proteins being considered the basic genetic material. In spite of its ideological bias, the USSR biochemical work on the nucleic acids and proteins, together with the knowledge displayed of the Western biochemical literature, seemed to indicate a potential for competent research on the chemistry of inheritance.

In a discussion by Rashba (1953) on the role of nucleic acids in the variability of microorganisms, the theme was largely anti-Weismann anti-Morgan. Michurin's concept was advanced and heredity was felt to be strongly under the influence of the environment. The transformation studies of Western scientists were characteristically used to support the concept of "environmental effects on heredity." Criticism of transformation experiments was mainly directed at the interpretation that DNA is to be equated with the gene and transformation with genetic transfer. This idea was thought to be "harmful and reactionary." Rashba expressed the view that DNA is important "not because it is a gene, but because it is assimilated by growing cells, and as each assimilated environmental condition, has its influence on the metabolism of the organism." He stated that it is the assimilation of the DNA and a subsequent replication of this similar DNA which brings about enzymatic changes, polysaccharide synthesis, and other alterations until one ends with "transformed cells." While this represents an excellent example of the tendency of USSR biologists to force data to fit an ideological concept, it nevertheless seems that the major difference between Western and USSR views at this time lay primarily in the manner of interpreting DNA transformations, i.e., transfer of a gene or hereditary factor vs. an environmental control of heredity.

Rashba recognized the "specificity" of nucleic acids, and felt that both substrate and nucleic acids "react on the proteins of the organisms," that is, on enzyme formation. Western scientists, on the other hand, talk about the "potential" of the genotype (as controlled by DNA) and the "expression" of the phenotype (as influenced by the environment, in this case, the substrate). They conclude, for example, that a cell genetically capable of forming an inducible or adaptive enzyme will do so only under suitable environmental conditions.

By 1956 there were indications from papers written by several authors (Dubinin, 1956; Loginova, 1957; Petrov, 1956–57; Belozersky, 1956) that considerable interest existed in the USSR in the subject of chemical genetics. It was noteworthy, however, that with few exceptions the majority of the work seriously discussed by these authors was non-Soviet research. When references to USSR work of a comparable nature were checked, the papers were found to be poor in quality (e.g., the "directed mutation" studies).

Dubinin's discussion included a thorough review of Western work to 1953, with full recognition of the importance of DNA. There was certainly familiarity with physical-chemical and biochemical

methodology (from x-ray diffraction to biochemical genetics, for example). The concept of DNA as a "genetic code," the transfer of "information," genetic fine structure and the problem of pseudoallelism (Dubinin's own early work on this is adduced), position effects, Goldschmidt's criticisms of the discreteness of the gene, and the idea of "sites" within the gene are all considered. If this review by Dubinin is to be taken as any indication of overall interest in the subject in the USSR, there may well be in the future a considerable emphasis on research in the field of biochemical genetics.

Loginova undertook to review the transformation studies and attempted to bring into the realm of scientific respectability the USSR work on "para-immunity," "mentor strains," "feeders," "filterable forms," etc. The Western literature from 1954–1955 was cited. Like some Western geneticists, the author was eager to attribute some genetic importance to the protein in the DNA transforming preparations of Hotchkiss and others (even if it represented only a 0.02% contamination). Some of the examples cited by Loginova, for example, Boivin's studies of transformation in *E. coli*, have not been confirmed, but by and large, the paper indicated a fairly broad knowledge of Western transformation work, including those on the competence of cells, speed of transformation, required exposure time to DNA, etc. The author questioned the validity of some of the Western transformation work in which there were "inadequate controls for contamination and spontaneous mutation." In the light of the present criticism of much of the USSR work evaluated here, this is rather humorous.

Several papers by Petrov were of some importance. In one paper (Petrov, 1956), work was reported on S^{35}-methionine experiments using a vitamin B_{12} mutant of *E. coli* which was obtained from the United States and which responded to both vitamin B_{12} and to methionine. The conclusion that vitamin B_{12} could eliminate the methionine requirement by permitting endogenous methionine synthesis was actually not as important as several other points. This was one of the few experimental papers in the present body of work in the area of biochemical genetics where there was evidence of technical competence as well as familiarity with Western methods, such as the penicillin method of Lederberg and Davis for selecting mutants of *E. coli*. In a later paper, Petrov (1957) discussed theories of protein synthesis, the template concept and its relation to DNA and RNA, and the relationship between the DNA template and the gene. He disagreed with views held by other USSR scientists that it is the constancy of certain environmental conditions which causes a constancy of chemical reactions, leading to transmissible hereditary properties. Petrov stated that the major contributions in biochemical genetics have been made "during the last few years through the study of microbial biochemical reactions controlled by separate genes." He also discussed the "one-gene one-enzyme" theory on the basis of Western work with *Neurospora*, and was familiar with much of the nutritional mutant work of recent years.

It should be emphasized that these papers of Petrov's afford the only reliable indication that biochemical genetic concepts and techniques are available and are actually being seriously employed in the USSR. Petrov, in fact, cited no other USSR work in this field. He clearly pointed out that "there is every ground for considering that the mechanism of action of the genes, which has been determined in the study of biochemical mutations in microorganisms, is not an exception, but a general rule for living organisms."

One may conclude that a USSR research effort in biochemical genetics may have begun by 1956, and that the Western literature had become available to a number of competent investigators at least by that time. Since biochemical work in the USSR appears in general to be competent (see Belozersky, 1956), the USSR potential for successful work in biochemical genetics may be good. Certainly, if the scientists interested in this area of research are able to carry on their investigations without undue political or ideological pressure, there is every reason to expect significant contributions from the USSR in this field within a few years. Also clearly, Soviet scientists in 1956–1957 were freer to discuss and publish controversial material than at any previous time during the present decade.

3. DRUG RESISTANCE AND ANTIBIOSIS

Research interests in this area have been largely devoted to a search for new drugs and antibiotics having antibacterial, antiviral, or antitumor activity; to comparisons of the morphological, biochemical, and immunological properties of strains, resistant or sensitive, to antibiotics or drugs; and to clinical work on the evaluation of antibiotics, including their therapeutic use singly and in combinations.

This area has undoubtedly been given high

priority in USSR microbial studies. The work has included studies on the chemical and biological properties of antibiotics and on problems of resistance to antibiotics, particularly among the enteric organisms and the streptococci. There are reports of many new antibiotics, e.g., uroformalicine (from garlic), a broad spectrum antibiotic reported to affect bacteria; trichomycin, reported to affect gram-negative bacteria, *Corynebacterium diphtheriae*, and certain dermatophytes; cerein B_2 derived from *B. cereus*, and reported to effect *Shigella*, *Salmonella*, *E. coli*, and *Serratia*; virusin 1609, an antiviral agent reported to be effective in preventing infection with mouse influenza A, A′, and B and against bacteria, actinophage, and epidemic encephalitis; usninic acid, derived from lichens, and reported to be effective against gram-positive bacteria, but not against fungi or yeasts; antivirubin, reported to affect tobacco mosaic and influenza viruses; mycerin, a polypeptide reported to have anti-pertussis, anti-*Salmonella*, anti-*C. diphtheriae* and anti-*Brucella* activity; and primicin, derived from actinomycetes, and reported to inhibit gram-positive bacteria. Various clinical studies were made of resistance and the use of combined antibiotic therapy, with attempts to compare results in vitro with results in vivo in clinical work; on methods of antibiotic assay and screening; on selection for vigorous antibiotic-producing microorganisms and new sources of antibiotics; and on synergism between non-pathogens and *Shigella*.

The range of interest in the general problem of "antibiotic research" appeared considerable, but it was also evident that much more emphasis was placed on applied aspects than on the more basic problems, such as the mechanism of drug or antibiotic action, the genetics of antibiotic or drug resistance, or the ecological aspects of antibiotic action and formation. An attempt will be made to evaluate some of the experimental work in this field and to indicate the research goals which have been emphasized by a number of the Soviet scientists by making a detailed discussion of several selected papers.

Besborodov (1957) compared a number of biochemical properties of certain antibiotic-resistant and sensitive strains of *Proteus morgani*. This work represented an attempt to characterize the biochemical changes which occurred in *P. morgani* following the development of resistance to several antibiotics: synthomycin, streptomycin, and chloramphenicol. Changes in DNA content, in the utilization of certain amino acids as nitrogen sources, in carbohydrate utilization, and in the activities of several dehydrogenases were reported. Unfortunately, the same defect already noted in much of the microbial work also obtained here, namely, a lack of quantitation. Even in respect to changes in enzyme levels, it was difficult to interpret the data in terms of specific activity, relation to growth, or other measurements. Hence, although scientists of the USSR undoubtedly recognize the importance of the problem of drug resistance, and have published many papers on that subject, the duplication of much of this work may prove difficult.

Some studies by Gauze (1956–1957) were of special interest. Some of his work on respiratory-deficient bacterial mutants has already been discussed, in a previous section. Gauze and his collaborators have screened various actinomycete products for antiviral activity against tobacco mosaic virus and influenza virus. They used a contact method of testing in vitro, and also in vivo methods. It is unfortunate that no data were given, but an antibiotic called Heliomycin was said to have some activity. Yet while the author reported some therapeutic effects of the antibiotic, he made it clear that effective antiviral antibiotics were still lacking, and that many additional antiviral studies would be required before success could be expected. In spite of the many names and descriptions of new antibiotics in USSR papers and abstracts there is no suggestion that effective antiviral antibiotics, which met the necessary in vitro and in vivo criteria for effective therapeutic use, had been obtained.

Markov (1955) reported the use of anti-penicillinase serum to restore penicillin sensitivity to staphylococci which were resistant to penicillin. In some instances bacterial resistance to penicillin was due to the action of penicillinase, the enzyme which destroys penicillin. Markov claimed that when penicilinase was inhibited by rabbit or mouse anti-penicillinase, the resistant bacteria became sensitive to the drug. The exact experimental conditions and quantitative data are not given. It is surprising that no mention was made of Pollack's contemporary work on penicillinase, since it would seem to have some bearing on these studies in the USSR.

An example of the ideological influence that has already been noted in several areas of microbial research in Russia is again to be observed in the work of Moroz (1956). This work concerned studies on the formation of antibiotic-resistant bacteria,

with emphasis placed on the "directing" action of the antibiotic. That is, "the resistance of microorganisms is a regular effect of interaction of the microbe cell with the medicinal substance, which changes the processes of metabolism and thus causes the formation of new resistant forms or death of the sensitive bacteria." The phenomena of stochastic resistance, mutation, and selection were interpreted as primarily reflecting the "directing" influence of the drug.

The influence of the agent on the origin of resistant bacteria is a problem that has received much attention in Western investigations. It is generally held that resistant cells arise by spontaneous mutation and that mutation can occur equally well in the presence or absence of the agent. Moroz has presented the results of tests on *Shigella*, *E. coli*, staphylococci, and *B. megaterium* with an actinomycete antibiotic called Grisemin. A two-fold serial dilution method of assay was used to determine the smallest quantity of Grisemin chloride which would completely inhibit growth. The resistance of cultures grown on low and high levels of the antibiotic was compared, and it was found that the resistance levels of the final population were higher in the latter case. Cross-resistance was reported with streptomycin, penicillin, aureomycin, and chloramphenicol. There was no indication whether this cross-resistance pattern was based on a single exposure to the antibiotics or was based on repeated subculture in the presence of the antibiotics. Changes in cell and colony morphology were also reported as occurring in those cultures exposed to Grisemin. The photographs supplied with the published material are, however, poor and not very convincing. Moroz claimed that the morphological changes were stable during storage for four years under vaseline oil. He also presented data which suggest differences in growth rate between the sensitive and resistant cells. Unfortunately, the curves shown reveal no individual points and no information was provided respecting the bacterium used, the number of experiments performed, or other essential matters.

The "biochemical differences" found in sensitive and resistant cells were expressed as "plus" or "minus" for such features as sugar utilization, indole formation, H_2S formation, or milk coagulation; it was almost impossible to tell to what extent these differences were associated with the mutation from grisemin-sensitivity to grisemin-resistance. No evidence was given to indicate that pure cultures were used, or that any of these "marker" changes were truly hereditary.

In a paper by Grunberger (1957) on the effect of albomycin on oxidative processes and nucleic acid metabolism in *S. aureus* and *E. coli*, the experimental methods appeared to be sound. Manometric technics, nitrogen determinations, optical density measurements of bacterial growth, nucleic acid determinations, and other standard methods were used. The report suggested that albomycin acts on nucleic acid metabolism and on the synthesis of enzymes concerned with nucleic acid metabolism. Albomycin treatment of cells resulted in the accumulation of acid-soluble nucleotides and nucleosides. Grunberger referred to Western work on penicillin treatment, in which similar accumulations have been noted. (This paper was probably written before the relationship between penicillin and cell-wall synthesis was reported in Western work, and a reason for the accumulation was proposed.) It should be noted that this paper was Czechoslovakian.

Krasilnikov (1957) reported on a new actinomycete antiviral antibiotic, "Luridin." He included a morphological description of the actinomycete, as well as the spectrum of activity of the antibiotic. "Luridin" is claimed to be active as an antibacterial, antifungal, antiyeast, antiphage (actinophage and *B. megaterium* phage) and antiviral agent. The virus tested was Grippe virus (influenza) A_1, and assay was by the chick allantoic cavity method. Actinomycete "culture fluid" was used as the source of "luridin." Virus propagation was measured after 48 hours at 37°C by an erythrocyte agglutination method. It was reported that 0.3 ml of "culture fluid" inactivated "100–1000 virus infectious doses," and that no correlation was observed between the antiviral and other antimicrobial activity. Some data were presented on the potency of the "culture fluid," determined by a dilution end-point method. However, the limited data and the lack of detail make this work difficult to evaluate experimentally.

Other interests seen in the USSR work on drug resistance and antibiotics included the resistance of actinomycetes to penicillin (where resistance seemed to be due to the destruction of the penicillin by actinomycete penicillinase), and the fixation of antibiotics by sensitive and resistant bacteria and by proteins prepared from them. The latter work indicated familiarity with the equilibrium dialysis method for measuring fixation and

with Pollack's work of the binding of S^{35}-penicillin. The author reported no difference between sensitive and resistant cells in their capacity to bind either penicillin or streptomycin.

Cytological and biochemical changes in *Streptomyces* during the course of streptomycin production were reported by Prokofieva-Belgovskaya (1957), and cytochemical and chemical analysis of RNA, DNA, nuclear size, amino acid composition, nitrogen, moisture, ash, etc., were carried out. The work appeared competent and the methods of analysis for sugars, amino acids, etc., indicated a familiarity with biochemical technics. It was concluded that streptomycin production is associated with older cultures, such as manifest a decreased growth rate, drop in RNA content, or decrease in certain amino acids.

Shorin (1953–1956) discusses methods of searching for antibiotics, with emphasis on the quest for antiviral agents, particularly those active against influenza virus. He reports that many actinomycetes secrete antiviral substances, and that twelve out of thirty preparations had anti-influenza activity in mice as well as in the chick embryo assay. The remainder were said to be either toxic or ineffective. Shorin emphasized the importance of using many different viruses for screening purposes and noted that a wide spectrum of activity could be found among antibiotics affecting viruses and bacteria; for example, anti-virubin is antiviral and also inhibits the growth of *S. aureus*. Eight other "antiviral" agents were listed. The author emphasized the need to develop antibiotics which would exert their antiviral effect while the virus was extracellular, before it had infected a new susceptible cell. The data are simply summarized, without experimental protocols or the results of individual experiments.

Zatulovski (1957) emphasized the caution which must be exercised in extrapolating from experiment in vitro to organisms in vivo the results respecting antibiotic efficiency, resistance patterns, cross-resistance, and changes in bacterial morphology, biochemistry, and immunology. He cited work on *Shigella* where cross-resistance was found between chloramphenicol and chlortetracycline in vitro, but where the testing of 123 resistant strains in vivo demonstrated no cross-resistance.

Sazykin (1955) summarized the results of a USSR Conference on Methods of Searching for Antibacterial, Antiviral, and Anticancer Antibiotics held in 1955, at which claims were made for actinomycete antibiotics having activity against bacteria, rickettsiae, some large viruses, small viruses, and malignant tumors. Plans for the study of antagonists were outlined, by means of "the separation of the cultures of microorganisms and the isolation of antagonists; study of the biological characteristics and evaluation of the antagonistic properties of the producers of antibiotics; the selection of fermentation media for promising cultures; the purification of the preparation from culture liquid; and the evaluation of the pharmacological, chemotherapeutic, and other properties of the preparation."

Emphasis was placed on "the use of test bacteria which are already resistant to most of the known antibiotics; on means for chemically characterizing the known groups of antibiotics; on the use of tobacco mosaic virus as a test virus rather than bacteriophages, which do not show antibiotic sensitivity similar to human and animal viruses." The following example was given. "The rate of coincidence of viricidal action of the culture liquid as tested on the virus of tobacco mosaic used as a model, and its action on the influenza virus reached the figure of 86%. A number of antibiotics selected by this method were found to have a more or less pronounced chemotherapeutic action on mice infected with the influenza virus."

Emphasis was also placed on the correlation between viral sensitivity in vitro and in vivo to an antibiotic preparation; on the methods used for cultivating the virus in vitro; on the difficulties encountered in anti-tumor work, namely, the lack of an exact knowledge of the etiology of tumors, and the impossibility in a number of cases of transferring to the clinic results obtained on experimental tumors; and on the methods used for testing anti-tumor activity, namely, the treatment of tumors with inhibitors and subsequent microscopic and macroscopic examination, examination of the tumor morphology and development in vivo, and direct tests on animals which have been infected with a specific type of tumor.

Finally, Grashchenkov (1957) reviewed the Second All-Union Conference on Antibiotics and the Principal Tasks in this Field. Certain trends and aims in this research area become apparent. Once again emphasis was placed on the search for new antibiotics, and a list of new antibiotics was included. The importance of studying the action of synthetic analogs was pointed out, and the use of one antibiotic ("Nistanin") was proposed "for the

treatment of complications caused by an overdosage of antibiotics (candidomycosis)."

The use of erythromycin for combating resistant staphylococci was noted, and the author states that "the application of new antibiotics (novobiocin and erythromycin) in combination with penicillin, as practiced abroad in the struggle against resistant staphylococci, points to a certain degree to the course to be taken in investigating and solving the problem."

Also mentioned by Grashchenkov was the fact that "the participation of representatives from foreign democracies and other countries, India, USA, accomplished a comprehensive interchange of ideas between the Soviet and foreign scientists." It was most interesting to note the editorial comments of the author, i.e., "these circumstances, in contrast to the first Conference, turned the present Conference on Antibiotics not only into a territorial—if the term is applicable to the vast territory of our country—but into a regional meeting of many countries of Asia and Eastern Europe. The numerous excellent reports presented by our guests gave the meeting the character of a large conference far beyond the boundaries of our country." This and other references seem to imply that many USSR scientists are in favor of more contact, discussion, and scientific interchange with the West. Certainly, a broad interest in antibiotics is evident throughout medical, veterinary, agricultural, and industrial circles.

Some references were made to successful therapeutic studies using combined antibiotic and bacteriophage treatment—"the combination of chlorotetracycline with bacteriophages proved very effective in experimental dysentery infections." In contrast, the therapeutic use of bacteriophage has met with little success in the United States.

The recommendations of the Conference for the future course of work in this area can be summarized as follows: intensive search for producers of antibiotics active against viral and fungal disease and against "various tumorous growths"; work on the biology, technology, and chemistry of antibiotic-producing agents and on the synthesis of antibiotic substances; increased production and lowered costs of antibiotics for medical purposes; investigations of combined prophylaxis and therapy using antibiotics, vaccines, vitamins, and phages; investigations of the mechanisms of action of antibiotics, and a "study [of] the pathogenesis of failure and complications due to microbial adaptation, allergic reactions"; the epidemiological significance of resistant microbes in various diseases; the introduction of the more extensive use of antibiotics in agriculture and in the food industry; and to improve the methods of cataloguing, and disseminating information about existing antibiotics.

It consequently appears that a major research effort has been proposed for work on antibiotics. Although much of this is applied in nature, there are still areas of fundamental interest in the program. It is difficult to tell whether the present Russian capacity in microbial work will be able to fulfill such a demand. The quality of much in this and in other areas of microbial research seems questionable. Whether the dearth of experimental data and detail observed in so many of the papers actually reflects a lack of technical knowledge and ability is a difficult question. With emphasis now being placed on greater cooperation and exchange between biologists, biochemists, biophysicists, and other scientists, there is a very good likelihood that the research will improve in quality.

4. SEXUAL RECOMBINATION

Very few reports were found in the USSR literature on sexual recombination in microorganisms. There were some references to "hybridization" of different strains of yeast, to "heterosis" between different strains of *Penicillium*, and to recombination in *Streptomyces rimosus*. In 1957 there was a brief report by Alikhanian on recombination between biochemical mutants of *S. rimosus*, and the author concluded that his results were similar to those observed by Western workers with other *Streptomyces*.

There was no indication of Russian research on bacterial or bacteriophage recombination anywhere approximating the level of Western research in this area. Tetrad analysis in the ascomycetes was not reported, nor were any reports seen dealing with linkage studies in any microorganisms. It would therefore appear that genetic analysis in microorganisms has received little attention by Soviet scientists doing basic research, and that the only consideration given to this area has been where certain applied aspects were involved, that is, increased antibiotic production in *Penicillium*, better industrial yeasts, and so on. It was apparent, however, from the USSR literature of 1955–1956, that early Western investigations in the area of bacterial and bacteriophage recombination had

gained the attention of numerous Soviet investigators. But it was not apparent from the source material whether they were aware of the relatively recent Western work on unidirectional transfer of genetic material from a donor to a recipient bacterium, the linkage relationships between prophage and bacterial genetic material, the use of transduction methods as a means of studying linkage relationships in bacteria, the concepts of gene "conversion," "copy-choice," and similar mechanisms, as means of explaining recombinations seemingly arising from noncross-over events.

5. GROWTH, CELL DIVISION, AND CELL THEORY

While it is beyond the scope of this review to discuss in detail the views of USSR scientists on problems of growth, cell theory, development and so forth, there are certain aspects of their interest in these basic problems in biology which have had a considerable impact on microbial genetics and on microbiology in general in Russia. The influence of the research conducted on "non-cellular living material" was noticeable by the early 1950's. The impetus was largely political-ideological, and the effect on the quality of research in many areas of microbiology seems to have been disastrous.

It may be worthwhile to review briefly the principal findings of O. B. Lepeshinskaya and her group and to point out the manner in which these researches influenced other scientific areas. The importance of this lies in the fact that USSR microbial studies related to microbial genetics appear to have been particularly susceptible to this influence for a number of years. It was during these years, in which Western studies in microbial genetics made significant strides, that the development of microbial genetics in the USSR came to a virtual standstill.

In the words of USSR reviewers, "the work of O. B. Lepeshinskaya (Stalin Prize Laureate) represented an important discovery in biology. She delivered a shattering blow to the reactionary cell theories of Weismann and Virchow and opened new prospects toward dealing effectively with a number of most important biological problems." The following paragraph summarizes one such study.

To demonstrate that life can originate not only from cells, Lepeshinskaya studied the regenerative properties of hydra. She used supposedly cell-free preparations of the disrupted organism that were obtained by differential centrifugation. The "lightest particles" were studied microscopically, and during the course of some hours the beginning of "cell development" (globule formation) was reported. This continued under conditions of proper feeding, namely, by daily additions of juice pressed out from Cyclops until, in the words of one reviewer, "the picture of the origin of life unfolded before us; life emerged visibly." On the basis of observations made using "slow-motion microcinematography," the following events transpired: "At the beginning, spots appear, then the spots grow, acquire brightness and coloring. Then we notice that some of the globules appear to become turbid. A dust-like granularity is produced in them. Three or four hours after the start of the observation, a brilliant vacuole can be seen in the grown globules. It grows and grows and finally turns into a nucleus. A cell has been born. Virchow's statement to the effect that the cell grows from a cell has been refuted." The Soviet author continued, "The cell originates without any divine command, and spontaneously. It is created as the result of the appearance of suitable relationships which are repeated, from day to day, from hour to hour, and every second, in different variation. This self-conceived cell lives, moves, now coagulates, then straightens out and revolves about its axis. Finally the cell begins to divide, at first in two, then each new cell also divides in two, and so on. Multiplication of cells takes place, the aim of this multiplication is formation of an organism. Finally, before the experimenter's eyes there appears a globule of 30–35 cells. Thus a living organism emerges. Lepeshinskaya experimentally proved the unforgettable words of Engels, that life 'is a process which is self-contained, intrinsic and innate to its bearer, the proteins.' It must be stressed that by her tenacious, carefully worked out experiments, accompanied by the ingenuity and cleverness characteristic of this particular laboratory, Lepeshinskaya has shown undeniably that the formation of new cells in the organism takes place not only by the multiplication of cells, but also by the development of cells from non-cellular living matter."

The studies of Lepeshinskaya's group also covered the role of living matter in the process of healing wounds, the development of blood islets in yolk globules of chicken embryo, and similar processes. Great importance was attached in the USSR to this work as can be seen from the following passage. "As early as 1945, T. D. Lysenko

predicted that Lepeshinskaya's work would become highly important. This prediction has now been fulfilled. Lepeshinskaya's work has great practical importance in a number of fields of science, primarily in biology and medicine. It has bearing on questions like the origin and development of malignant tumors, inflammation, regeneration of tissue and recovery of organs, etc."

It was not until about 1955 that the first severe public criticism of the work of the Lepeshinskaya group became apparent. In a paper entitled "The New Cell Theory and its Factual Basis," Zhinkin and Mikhaelov (1955) deplored the state of scientific research in this area and expressed their opinions vociferously and unambiguously. They cited repeated instances where USSR investigators were unable to repeat the work, or were able to attribute the observations on "formation of cells from noncellular living matter" to entirely different causes, and asserted that "there was no basis for calling the bodies observed as living or to justify their being called cells." In a flat statement on the entire research in this area, the authors stated, "Thus, the basic material underlying the new cell theory does not stand re-examination. It is not founded on solid, firmly established facts, and consequently, does not reflect any laws actually existing in nature. The hypothesis advanced by O. B. Lepeshinskaya can only claim to depict her own personal, subjective views and those of her supporters."

The work on the "New Cell Theory," dating back to about 1939, and criticized intermittently and ineffectually by some USSR scientists, was apparently under serious attack by 1955. However, even as late as 1956–1957 the influence of the "New Cell Theory" was still apparent in microbial work, particularly in reference to the "filterable forms" of microbes and their importance in microbial genetics, medical microbiology and immunology, and in industry.

It was suggested at the 1956 Conference on Filterable Forms of Microbes at the Institute of Experimental Biology of the Academy of Medical Science of the USSR that the name "filterable form" be changed to "living substance of microbes, which does not have a cellular structure." The following passages, quoted from a report of this Conference, indicated the trend of thinking in this area. "The living substance of microbes can be detected in cultures of any age without other additional injurious reactions. The basic physiological cause, which assists in the appearance of living substance in cultures, must be considered the physiological aging of cells, which is accompanied by their loss of multiplication function and autolysis. All the harmfully acting factors, both the natural (biological) as well as the artificial, only force the decomposition of cells and the release of living substance. The living substance of microbes possesses a greater resistance to harmful physical, thermal, chemical, and biological factors, than the cell forms. Nevertheless the limits of resistance must yet be experimentally established. During the process of development of cells from living substance there takes place a passage through several phases (stages), which are characterized by morphological, biological, biochemical, and antigenic properties specific for each stage. The initial stage of development of microbe cells of different kinds from the living substance is characterized by the community of a series of features independent of the species to which it belongs; formation of the species specificity of the developing cultures occurs during the following generations. In this case, there can take place both a reversion to the initial species through a series of intermediate forms, corresponding to phylogenetically earlier species, as well as a formation of other species, depending on conditions under which the development occurs."

"There exist two basic points of view on the question of the nature and of the biological sense of the living substance of microbes which do not have a cellular structure. First, the development of microbe cells from the living substance represents a result of adaptable variability of cells to unfavorable conditions of existence, and second, precellular living substance of microbes represents an initial stage of their ontogenic development."

The Conference group made several recommendations concerning the continued study of "microbial non-cellular living substance." These included "a further development of methods necessary for a productive study of the problem; studies of mechanisms of formation of the living substance, of its accumulation and its forcing of development of microbe cells from the living substance; demands for unconditional authenticity, provisions for controls and the highest approximation to natural conditions must be required of all methods; special attention to further development of research on the living substance of microbes, as applicable to diagnosis of infectious diseases, their pathogenesis, immunogenesis, and prophylaxis."

The long-range views of the Conference were to "take into consideration the special plasticity of cultures, which develop from the living substance, in order to utilize them to try to obtain living vaccinal strains; to recommend continued support (next Five Year Plan) and the organization of a methodical coordination center on the studies of problems of development of microbes from living substance," and finally, "to ask the Organization Committee of the All-Union Convention of Microbiologists, Epidemiologists, Infectionists, Hygienists, and Sanitary Doctors to include the Conference report on the development of microbe cells from living substance as one of the basic reports on the program question about the variability of microorganisms."

Hence, it was clear that considerable emphasis had been placed on this phase of research in USSR microbial studies. As pointed out earlier, these views on the importance of "non-cellular living substance" had a marked influence in many microbial laboratories in the USSR as late as 1957.

In the remaining discussion, a number of papers will be used to illustrate certain aspects of the research on "non-cellular living material." Additional reference will be made to this subject in the later section on Host-Parasite Relationships, Medical Microbiology, and Immunology in this review.

Kalina, in a paper published in 1953, discussed the problem of the "Phase Development of Microbes as an Objective Reality." Experiments were cited in which a phage lysate of *E. coli* was used for the study of "pre-cellular forms." No experimental details or data were presented, and evaluation of the worth of the material is impossible. There were no indications of the use of controlled experimentation, pure culture methods, or other standard procedures.

Kolesov (1954) reported on the isolation and regeneration of filterable forms of anthrax microbes from anti-anthrax sera. His work, as well as the numerous citations to other USSR studies, indicated considerable interest in the study of the "non-cellular living substance" of virulent bacteria, such as mycobacteria, salmonellae, shigellae, corynebacteria, and anthrax bacilli. However, the meager experimental data this author provided, and particularly the lack of detail in stating the experimental procedures, made the work virtually impossible to attempt to reproduce.

A paper by Solntseva (1953) on the methods for investigating filterable forms of bacteria provided a typical example of the problems raised by this type of research. Many of the experiments involved mixed cultures, microscopic observations, incubation periods of several weeks duration, and lack of a defined medium or use of any quantitative microbiological technics. The impression one received after reading numerous reports of this sort was that this area of research abounded in mysticism and virtually uncontrolled scientific experimentation. In a paper by Shchukin (1957), for example, on the development of colon bacilli from filterable forms, the author followed the "regeneration" of cells from phage lysates microscopically. Although this is an "experimental paper" no data were supplied and there was no indication of the author's familiarity with quantitative methods for measuring bacterial growth, or with current quantitative technics for handling bacteriophage.

While the USSR scientists may have unpublished evidence to support their claims, the published material here surveyed did not justify claims for the existence of a "living substance of microbes having no cellular structure." Furthermore, while references were occasionally made to advances in Western microbial methodology, there was no indication that USSR scientists in this area of research were employing these methods. It may be that in some instances the USSR investigators were actually dealing with bacterial protoplasts, or L-forms, but such a possibility was difficult to judge on the basis of the published material.

6. EVOLUTION AND ECOLOGY

Of considerable interest to USSR microbiologists was the problem of microbial species formation. Underlying most of the published work was the controversy between the pro- and anti-Lysenkoists, particularly over the importance of the role of natural selection in species formation. As late as 1956 Lysenko maintained that his purported "new species" were not the result of hybridization, but resulted from the "generation of one species by another." This entire conflict undoubtedly had a major influence on the work dealing with "the experimental conversion of one species of microorganism into another," which has occupied USSR microbiologists for some time.

The microbial work appeared to be an outgrowth of Michurin's biological concepts, heavy emphasis being placed on the phenomenon of "directed modification" in the formation of new

species of microorganisms. Much of the work in this area was devoted to pathogenic microbes.

In a discussion paper by Muromtsev (1952), the author stated that "Darwinism dealt the final blow to the anti-scientific, religious idea dominating pre-Darwinist biology that the species in nature were each created separately, not connected with each other in their origin, and that they were everlasting and unchanging. This metaphysical idea was replaced by Darwin's theories. Darwin, however, did not arrive at the truly scientific ideology of dialectical materialism. Michurin, led by dialectical materialism, demonstrated that the development of living nature does not take place in the manner described by Darwin in the *Origin of Species*, i.e., that transmutation of species does not require thousands of years." Summarizing some of the results of plant studies, the author continued, "All these similar facts, observed in the past and recently cleared up, have produced a new explanation important to science and to practice which leads to the fact that the origin of various contaminations and some impurities of crops, except for those frequently introduced by mechanical means, may be the generation of one species of plants by another species."

Muromtsev asked, "What facts can be cited from the field of microbiology which give us the right to state that transmutation of one species of microorganism into another species can be observed and even produced experimentally?" He cited, among other examples, the modifiability of enteric microorganisms in outbreaks of gastrointestinal diseases in human beings and animals, and in enteric microorganisms in the water supply; the modification of human plague bacilli into cells resembling "pseudotuberculosis microbes of rodents," i.e., having similar morphological, cultural, and enzymatic properties. Similar work was included on the transformations involving pneumococci, beta-hemolytic streptococci, and *Streptococcus viridans*; of true and pseudo-diphtheria bacilli; and of anthrax bacilli, clostridia, *H. pertussis*; etc. This publication contained no experimental data, and yet the author stated, "The *factual material* presented above leaves no doubt that Lysenko's rules of species formation in higher plants have also been fully verified on microbiological objects. It must be realized that the view prevalent to microbiologists to the effect that existing species of microorganisms were created only in the remote past and that none are being created at the present time is unscientific."

Quoting Lysenko, Muromtsev continued, "Changes in the conditions of the external medium responsible for the species characteristics of given organisms will sooner or later compel a change in the species characteristics—one species generates another. Under the influence of conditions which have changed and have become unfavorable to the nature of organisms, rudiments of other species which are better adapted to the changed external conditions are generated in the body of the organisms of these species."

The importance of a "living substance of microbes having no cellular structure" was again emphasized. "In the development of pre-cell filterable forms (see the preceding section), as a rule, cells are obtained which in some properties differ to a certain degree from the original microbe culture. This has been observed by every microbiologist who has ever worked with filterable forms of microbes. The first generations of microbe cells obtained through regeneration of filterable forms, the so-called secondary cultures, have the capacity to revert to the original type, but on the other hand, are much more easily subjected to further change as far as the species characteristics of the original microbe are concerned. Therefore, microbe cells from secondary cultures are particularly suitable for profound directed modification of the nature of microbes."

It is interesting that in the instances in which the "agent of pseudotuberculosis of rodents was obtained from cultures of plague bacteria, or in which the dysentery microbe was turned into the paratyphus microbe . . . the action of a specific phage on the original culture was used." It was further pointed out that "the transformation of ordinary visible microbes into the pre-cell forms is also accomplished by means of other actions exerting an unfavorable influence: repeated freezing and thawing, action of specific bacteriolytic sera, antibiotics, antiseptics, various salts and prolonged storage of a culture without re-seeding."

Muromtsev continued, "The methods of regenerating pre-cell forms have also been developed to a higher and higher degree. It is extremely important to learn to conduct the regeneration of the pre-cell forms and the raising of the first generations of secondary cultures under conditions which would guarantee the purposeful change in the nature of the microorganisms required by practice. Of course it is impossible to indicate or foresee the conditions and the time of breeding,

the number of changes of generations, the selection of the original culture, etc., for any microbe."

It is important to mention that, in a gross sense, some of these reports could be interpreted on the basis of such phenomena as transformation, transduction, or lysogenization. However, both the information provided by USSR authors on the experimental procedures and the data supplied are insufficient to permit a definite conclusion. Muromtsev surmised that "the disintegration of microbe cells under the influence of unfavorable conditions takes place not only in artificial laboratory surroundings but literally anywhere in an external medium in the soil, in water, and in the organism of plants and animals. If we consider this, it must be realized that the process of development of pre-cell forms of microbes under conditions which are not favorable to the nature of the old species, i.e., to its heredity, is the main source of the formation of new stocks and species in the world of microorganisms."

A number of methods were suggested for the development of pre-cell filterable forms into microbe cells, for example, growth in the presence of "feeder strains" (sarcina or staphylococcus) to provide essential substances for the development of filterable forms, the use of an emulsion of dead microbes, prolonged growth (for several weeks) at different temperatures and animal infection with material containing filterable forms.

Reports of this sort were evident in the USSR literature until 1955, and judging from the more recent abstracts, work in this area has continued. Sosov (1955), writing on the theoretical significance of the problem of the species-forming variability of microorganisms, emphasized the importance of studies of this type for understanding the origin of infections.

Turbin (1954), in an important critical discussion entitled "The Peculiar Methods of Proving the New Theory of the Formation of Species," opposed the Lysenkoist views of the obscure or needless role of natural selection, although the Michurin concept of "the regularities of predetermined variability" was still maintained. Turbin expressed strong views on the suppression within the USSR of work in certain scientific areas, for political and ideological reasons. He stated that "the history of biological science knows of no theory which, being a truly scientific theory, would require for its consolidation any measures aimed at protecting it against criticism, and still less of persuasion means, having nothing in common with science but intended to establish its correctness by deliberate distraction and even intimidation of all those who hold different views. Only people who are uncertain of the correctness of their views, in the conclusive nature of the theoretical propositions advanced by them, are in fear of conflicting opinions and resort to justification methods which have nothing in common with scientific methods of establishing the truth." This paper, we may note, was written by Turbin to refute some accusations of Studitskiy (1953) that he (Turbin) had "attempted to defame the fundamentals of Michurin's biology." Studitskiy was of course a strong pro-Lysenkoist.

Turbin made a further interesting statement indicative of the current state of affairs of USSR genetics. Though critical, he apparently was fully aware of the need to support certain basic Soviet doctrines. He said, "The work of T. D. Lysenko as a leading scientist in Michurin's genetics I have always valued very highly, and his attainments in the development of Darwinism, in particular as it concerns elimination of the defects found in this theory, have been repeatedly noted in my contributions, etc. My pronouncements are against the theory of formation of species advanced by Lysenko (i.e., that the development of living nature takes place by generation, under altered conditions, by one species, of organisms of another species). This is supposed to take place due to the fact that under these conditions there are formed within the individuals of the old species body particles having new species qualities, in which the old quality elements are at once and simultaneously replaced by elements of the new species quality, as a result of which such individuals of one species generate directly individuals of another species. For example, it is being asserted that in this manner, under specific conditions, rye can become within 2 to 3 years brome grass, wheat, or even wild oats, and wheat can be transformed into rye, barley, oats, wild oats, etc., a theory which in my opinion is erroneous and not in accord with facts and theoretical propositions of Michurin's biology."

Turbin continued, "This does not signify that I abandon the fundamental propositions of Michurin's biology, the criticism of Weismannism-Morganism, and all to which was dedicated my scientific career. Just as unsubstantiated and distorting the facts of the situation are Studitskiy's assertions purporting that I accuse Lysenko of Weismannism and idealism, and alledgedly deny changes of heredity through assimilation by the

organism of altered life conditions and the principles of the inheritance of acquired characteristics and others."

Turbin supported the view that "Lysenko has no facts relating to new formation of species and that all which is involved is only indirect proof of the general universal nature of the processes of generation of one species by another." In discussing Studitskiy's attack, he stated, "Furthermore, Studitskiy declares with indignation that 'demanding from Lysenko direct, factual proofs in support of his views concerning the formation of species is unjustified, since a process occurring in nature over hundreds of thousands of years cannot be demonstrated to anyone for the asking.' Thus so far we were told of a theory which has demonstrated that within 2 to 3 years one species may be transformed into another, and thus new species are formed which, it is alleged, can be ascertained, from facts, by anyone who has doubts; now we find that hundreds of thousands of years are involved." Turbin continued, "Further on we find an even more remarkable admission, namely, how very perplexing is for instance the process of reverse transformation of the new species into the old one which had generated the former. It is not understood how one species can arise by being generated by many species. These processes are indeed in conflict with the concepts concerning the irreversibility of development and monophyletic evolution, which are firmly established in the literature of Darwinism." Turbin concluded his lengthly discussion with a hopeful statement, "Time is the best friend of truth."

It is quite clear that the concepts of Lysenkoism, arising from agricultural work, had much influence on thought in the field of microbial genetics. However, between 1952 and 1954 there were some opponents of these views who publicly tried to place USSR genetic studies back on a more sound experimental foundation. The microbiological investigations in this area were subject to the same objections raised against the agricultural work, specifically, the lack of well-established experimental results carried out under scientifically controlled conditions.

There is experimental evidence from Western microbial genetic work for the existence of DNA transformations between pneumococci and *Streptococcus viridans*, for genetic exchange between different enteric microorganisms and for conversion of avirulent to virulent diphtheria bacilli by lysogenization with a specific bacteriophage. On the other hand, Soviet scientists offered little evidence, other than ill-defined statements, that any valid experimental basis actually exists to support their views on microbial species formation.

7. METABOLSIM AND PHYSIOLOGY

There are several important points to be brought out about investigations in this area. The calibre of the experimental studies relating to the biochemical aspects of microbiology appeared to be higher than in the biological work. It seemed that technically and conceptually, biochemistry in the USSR was in a more advanced state than microbiology. For example, the work of Khesin and his collaborators (1955) dealt with protein synthesis in cytoplasmic particles isolated from liver cells, and the authors were familiar with technics employing complete amino acid mixtures, ATP, microsomes, mitochondria, etc. Work was reported on the action of chloramphenicol on endoproteases and glycolytic enzymes (1956); on amino acid analysis in yeast; on the use of S^{35}-sulfate, C^{14}-amino acids and S^{35}-methionine, to study amino acid incorporation and turnover in ovalbumin (1955); on methods for the isolation and purification of streptococcal hyaluronidase; on studies of the intermediary metabolism of pentoses in mycobacteria; and on changes in catalase levels in plague and pseudoturberculosis organisms after animal passage. These reports all pointed toward the use of reasonably modern biochemical methods and approaches.

One research area that was lagging was the study of induced enzyme formation in microorganisms. There were indications that some work of this type was being carried on in USSR laboratories, but the studies appeared to be of the applied type. No evidence was available to suggest that any experiments had been designed to use induced enzyme formation in microbes as a model system for investigating problems of protein biosynthesis.

Work reported by Demyanovskaya (1957) on the effect of oxygen on actinomycete DNA attempted to show that actinomycete DNA was qualitatively different from thymus DNA (on the basis of different extractability in the presence and absence of oxygen). While the data were not too convincing on this point, it seemed that reliable nucleic acid extraction and determination methods were familiar to the investigator.

In certain types of research, insufficient controls

and data still constitute a basis of major criticism. For example, Elin (1957) reported on the growth of heterotrophic bacteria on a medium deprived of organic matter. He concluded, on the basis of inadequate data, that certain heterotrophs (*E. coli*, *Bacillus pyocyaneus*, *Proteus vulgaris*) could grow in a medium containing only inorganic salts while using "volatile compounds in the air" as carbon and energy sources. No evidence was presented to support the claim that carbon dioxide was not utilized, and no quantitative estimates of the extent of growth were given.

In a discussion by Kriss (1954) of USSR work on the microbiology of cellulose, in investigations of energy metabolism in heterotrophic bacteria by Manteyfel (1949), and in a report by Paliy (1952) on the growth of microorganisms under reduced pressure, there was no indication of the ideological motivation felt so strongly in other areas of microbial work.

Medvedev (1952) discussed the problem of the dynamic state of proteins, citing Western studies by the Schoenheimer group, Shemin and Rittenberg, Anfinsen, and others, on this general problem. The presentation was reasonable and devoid of any serious ideological overtones.

Consequently it appears from scanning some of the biochemical work in the USSR that biochemistry was generally in a more favorable position than microbiology. The reports indicated familiarity with modern biochemical methods, data were frequently presented, and the discussions did not contain the plethora of Soviet doctrine emphasized in many of the other papers reviewed. If the scientists in the more biochemical aspects of microbiology possess sufficient prestige, perhaps their influence may be felt in microbial genetic work. This possibility has been discussed in the section on chemical genetics.

8. HOST-PARASITE RELATIONSHIPS, MEDICAL MICROBIOLOGY, AND IMMUNOLOGY

In discussing this research, which in itself covers a broad range of subjects, the material has been subdivided into bacteriophage work, studies on animal and plant viruses, and non-clinical and clinical work in medical bacteriology, mycology, and immunology.

It might be helpful to indicate the type of work that was published from 1955–1957, as judged by the latest available abstracts on USSR research in these areas.

(a) Bacteriophage studies: quantitative studies on media factors affecting bacteriophage formation; lysogeny among shigellae and the influence of anti-dysentery phage sera in causing lysogeny; the effect of *E. coli* phage on *Salmonella* and *Shigella*; antigenic properties of *Salmonella* phage; effect of antibiotics on phage; the use of dysentery phage for the diagnosis of suspected *Shigella* cultures; the effect of phage in producing "filterable forms" of typhoid bacilli; the use of *Shigella* phage for therapeutic purposes, and the problem of phage-resistant bacterial mutants; studies in enzyme activity (catalase) in actinomycetes following phage infection; and finally, the use of phage in industry.

(b) Animal and plant viruses: the artificial synthesis of viruses—the reconstitution of polyhedral virus from non-infective protein and nucleic acid; discussions of tobacco mosaic virus reconstitution; the mechanism of virus infection; the physiology of plant viruses; cultural conditions for obtaining influenza virus with polyvalent antigenic structure by mixed infection with two virus types; studies on clover mosaic virus; properties of rabies virus; studies on receptor substances which possess substrate properties for virus enzymes; electron microscope studies of influenza virus; anti-metabolites and the reproduction of tobacco mosaic virus; preparation of smallpox virus vaccine; biophysical studies of viruses; virus studies and trachoma; serum and infectious hepatitis.

(c) Medical bacteriology, mycology, and immunology: biochemical and cultural characteristics of pasteurellae; the purification and isolation of the Vi antigen of typhoid bacilli; epidemiology of coli enteric infection; identification of brucellae; the hemagglutinating activity of pertussis extracts; studies on the variability of anthrax vaccine strain; diseases caused by salmonellae; toxic properties of hemolytic and viridans streptococci isolated from scarlet fever cases; the variability of enteric pathogens; animal susceptibility to staphylococcal enterotoxin; diphtheria and the dynamics of the infectious process; the use of fish wastes broth as a high toxin-producing medium for diphtheria bacilli; sanitary bacteriology and the survival of dysentery bacilli in reservoir water; the growth of dermatophytes; Candida transmission; the yeast flora in certain skin infections; the distribution of yeast-like fungi in organs; experimental studies of blastomycosis; anti-fungal agents; alpha-globulin in the prophylaxis of infectious hepatitis; antipertussis vaccine and inoculation against pertussis;

immunological studies on purified absorbed diphtheria toxoid; tissue transplantation work and discussion of the homograft problem; tularemia and plague vaccination; brucella vaccination; the use of antigen-antibody diffusion in gels for immunological studies; and immunological changes in "directly altered" enteric bacteria involving nucleoprotein fractions.

In the discussion which follows, an attempt has been made to cite a number of pertinent papers in the areas of bacteriophage and animal and plant virus work, as well as in medical microbiology and immunology, and to discuss the progress of this research in more detail.

Boshyan (1950), in work on the nature of viruses and microbes, reported the transformation of a virus causing infectious anemia of horses into a visible microbe. This work was published during the height of the "filterable form" studies in Russia. The author claimed that these microbes could be grown in an artificial culture medium, and that the microbial and virus forms were capable of transformation into each other and also were reversibly transformed into crystals.

Furthermore, Boshyan stated that "when a pathogenic microbe penetrates into the body of an animal, the microbe's cell breaks down into its component parts and assumes a filterable form, i.e., the microbe becomes a virus. On breaking down, the microbes become less pathogenic or nonpathogenic and assure immunity to the animal. In other words, the microbe is transformed from an antagonist agent into a living substance associated with the host, this process at the same time safeguarding the survival of the microbe. Contrary to accepted views, a sharp line between parasitism and saprophytism cannot be drawn; there is always mutual adaptation. The interconversion of filterable viruses and microbes is not accidental, but quite general and represents a universal biological law. The virus forms and microbe forms of the same species undergo evolution into other species in the process of interconversion. The isolation of initial microbe forms from filtrates of cultures causing typhoid, brucellosis, tuberculosis, anthrax, tetanus, dysentery, paratyphoid, diphtheria, and other diseases proves that microbes are capable of transformation into a filterable form (virus) and that the division into viruses and microbes is entirely artificial."

Boshyan continued by stating that "it is wrong to assume that viruses, as distinguished from microbes, are incapable of propagation outside of living cells and that they may live only as intracellular parasites in the organism of host plant and animals. They do develop and propagate in artificial media as long as nucleoproteids are present. The metabolism, division, and propagation of viruses proceeds by way of crystallization. The virus nucleoproteid is the basic protein from which all forms and species of microorganisms are formed."

Boshyan's further comments on the problem of immunity were also revealing. "Any immunity, no matter against which infection, is a non-sterile, infectious immunity. In an immunized or hyperimmunized organism the microbes do not disappear, but are transformed into a virus or phage form which is inactive and does not cause infection. An immune or hyperimmune serum, when introduced into the animal, transforms the microbe cells which are present in the organism into a phage or virus form. A bacteriophage performs the same function; it transforms the microbes into another phage form, one of the forms which combine readily with blood proteins. The virus or phage form of microbes combines with the proteins of the animal organism, as a result of which neutralization of the virus or phage takes place. Immunity against viruses as well as microbes is conferred in this precise manner. On penetration of microorganisms into the body the proteins of the body change their configuration in such a manner that they acquire the capacity to combine with virus or filterable form of the microbe in question. In other words, antibodies are simply a combination of modified protein substance with the filterable form of the antigen. When the filterable modification of the microbe or virus disappears, the protein in a special antibody state can no longer form or exist in the organism."

The impact of the Lysenko-Lepeshinskaya ideology on USSR microbial work in the period around 1950 can be readily seen from the preceding material. In all of the work just quoted, it was impossible to find any convincing data or detailed protocols for these experiments. Furthermore, by 1955–1956, this work of Boshyan was under severe attack by many of his scientific colleagues. In fact, while several studies of this type were published during 1952–1953, the main trend by 1954–1955 was clearly away from such work.

In a report by Fisher (1950), the phenomenon of the "nature of sterile spots" was discussed. The

work concerned studies on plaque formation, the distribution of phage particles, etc. There was no indication in this paper that the investigator had any knowledge of quantitative procedures for studying bacteriophage as, for example, the one-step growth curve or plaque-counting methods. A similar situation was noted in work by Kanzanskii (1952) on the action of chemical substance on viruses. This author used a method of bacteriophage inactivation to screen for antiviral agents (organic and inorganic), but the methods were totally devoid of quantitative measurements—the use of "so many drops" of the phage preparation alone denoting quantity. It would be difficult to repeat this work on the sole basis of the details stated in the paper.

Hercik (1953) discussed the macromolecular structure of bacteriophage. While aware of current Western work on phage genetics and lysogenicity, he disagreed with many of the findings, particularly those relating to phage recombination and its genetic interpretation. Hercik reported the results of electron micrographs on phage infection of bacteria and in general agreed with the sequence of events described by Western authors, adsorption, penetration, etc. However, his interpretation differed at one crucial point, namely, where he stated that "we cannot consider bacteriophage to be a parasite, but that in all probability it is an existing form of bacteria. However, neither can it be said that bacteriophage is a definite step in the formation and development of bacteria. It seems that a bacterium can change into a bacteriophage only in rare instances, and only when an inducing phage or a physical factor, such as the action of ultraviolet light, changes its metabolism in such a manner that it changes itself completely into bacteriophage." It would seem that although Western and Soviet interpretations of these phenomena differed in 1953, the USSR scientists were nevertheless conversant with new technics and ideas in this area of research.

Kriss and his collaborators published in 1952–1953 a number of electron micrographs of phage structure. They interpreted their results as supporting the view that the phage head contained mainly coiled (spiral) globular protein molecules, and that the coiling was influenced by the nucleic acid residues in the head. They felt that this coil continued from the head of the phage particle, and that the free end of the coil represented the phage tail. (Interestingly, they used high concentrations of urea to produce inactive phage lysates. It might be noted that urea is currently being used in a number of Western laboratories as an agent for disrupting hydrogen bonds and as a reagent for preparing disrupted phage particles.) These preparations contained small granules equivalent in size to the globular elements forming the phage head. This Soviet group also described electron microscope pictures of disrupted phage tails in which a thick casing surrounds a fine filament. The results were strongly suggestive of recent observations in this country on the fine structure of bacteriophage. It would seem that these USSR investigators were technically capable, and it would be very interesting to see some of their more recent results.

A paper on true lysogeny in the actinomycetes was published by Rautenshtein in 1957. The work was interesting, since the author appeared conversant with numerous current studies on lysogenicity, phage technics, and similar matters. The various indicator strains of actinomyces were screened by using an agar block diffusion method. The data were recorded as "plus" or "minus" for the activity of a particular actinophage on a particular actinomycete, but for this type of study such data were adequate. The studies showed the polylysogenic nature of some of the actinomycetes, as well as the interaction of the phage and the host cell in influencing phage host range. The paper indicated a familiarity with the Western scientific literature, and an interest in phage as an experimental organism. However, even in 1957, there was no evidence of extensive USSR work in the area of phage genetics.

Kleyn (1954), in a discussion of the biochemistry of bacteriophage, indicated familiarity with the Western work up to about 1951. He discussed the effect of bacteriophage infection on bacterial carbohydrate decomposition and enzyme activity, the role of cofactors such as calcium and tryptophan in phage infection, and the question of the source of phage nitrogen, carbon, and phosphorus. While giving no data on USSR work, he stated that results comparable to the Western work had been obtained by Russian investigators.

In another paper by Kleyn (1956), the synthesis of viruses was discussed, with particular emphasis on the reconstitution of tobacco mosaic virus from RNA and protein. Kleyn criticized the work of Fraenkel-Conrat and Williams on what seem to be unjustifiable grounds, such as that "the research

will require repeated checking, since microbes visible under the light microscope can take up invisible forms." Hence, the "filterable form" problem was introduced by this USSR investigator, who suggested that TMV may have disaggregated to form filterable, invisible material. There were no experimental grounds for such an interpretation based on any USSR experimental work. Kleyn's paper lent support to the view that there has been an increased USSR interest in the nature of phage and viruses, and in obtaining Western literature on the subject.

In several papers (1953–1955), Sukhov discussed the nature of viruses and the mutability of viruses in mixed infections. The work published in 1953 emphasized the importance of viruses as organisms precellular in nature, but bearing no relationship to the "filterable forms" of bacteria. The conflict between the USSR scientists on the concept of viruses as "living organisms" vs. "non-living infectious agents" was apparent, and emphasis was placed on the protein components of the virus as the important factor in infection. Sukhov argued for recognizing viruses as living organisms, but of a precellular type. "Viruses, like all living beings, are capable of reproduction. Proliferating under the constant conditions of a culture medium, viruses persistently preserve the characteristics of their species (exhibit the capacity to inherit and transmit species characteristics). The use of radioactive isotopes permits us to conclude that virus particles carry on an intensive metabolism, using the substances of the cells which they inhabit."

It can be seen that some of the rudiments of contemporary virus work had begun by this time, but certainly there was a considerable lag in virus research and in developing concepts of virus biochemistry and genetics.

In 1955, Sukhov reported on mixed infection using two related strains of tobacco mosaic virus. The paper referred to Western work on phage and virus recombination, but the author refused to consider bacteria and viruses as representing sexual organisms. Emphasis was placed on the "mutual exchange of substances" similar to "vegetative hybridization," rather than genetic recombination. In the author's discussion of the mixed virus infections, it became apparent that some of the Western and USSR views were slowly converging. For example, "even at the level of the non-cellular forms, which the viruses are, the formation of a posterity is as a rule connected with the known multiplicity of forms which take part in this process. All the advantages which the sexual process gives to the more highly developed organisms find their places in the reproduction of primitive forms of the virus, the organization of which grants an extensive process of mutual interchange between particles at the moment of reproduction. We suppose that even the sexual process itself has as its source this primary biological need of mixed heredity in the formation of a posterity. The metabolic reactions found in viruses and the sexual process in cellular organisms are in no way remote from each other; they express one and the same principle of living nature and represent different forms of a synonymous biological process."

A discussion paper by Solovyev and Zhdanov (1954) was worthy of attention, since the authors indicated what they felt to be "the most important tasks of USSR medical virology." Emphasis was placed on "problems pertaining to the modifiability, morphology, and biochemistry of viruses and to the experimental chemotherapy of virus infections." The effects of prolonged animal passage on the immunogenic characteristics of viruses were discussed, and the importance of understanding the viral changes in connection with the production of live vaccines was emphasized. Particular attention was paid to studies aimed at obtaining live vaccines for the prophylaxis of influenza. The studies on the morphology and biochemistry of viruses were to be centered on the "morphology of viruses and of virus inclusions by means of electron microscopy and phase-contrast microscopy. This is of great importance for the clarification of the nature of viruses and the diagnosis of virus infections." The biochemical studies were to concern the chemical nature of viruses themselves, and the "biochemical processes which take place during the reaction of viruses with sensitive tissues of the macroorganism being investigated. This opens up the possibility of finding methods which make it possible to influence the process of infection by chemotherapeutic means." The authors stated that "the most important task which confronts Soviet virology is the practical solution of the problem of influenza."

In work reported by Tovarnitskiy and Vorobyeva (1954), the effect of ATP (adenosine triphosphate) on the reproduction of influenza virus was studied. In view of the importance attached to the influenza problem by Soviet scientists, this paper was of some interest. The purpose of the experi-

ment was to study the effect of the direct introduction of ATP on the multiplication of influenza virus in human embryo lung tissue and mouse embryo lung tissue. Influenza virus multiplication was also studied in de-embryonated eggs by using a chorioallantoic membrane method of culturing the virus. The authors claimed that ATP increased the virus yield 1–3 logarithms in most cases. They were aware of Western and USSR studies on the inhibitory effect of 2,4-dinitrophenol on virus multiplication, and concluded that the "participation of ATP in the synthesis of viral nucleoproteins may be considered entirely probable." The importance of this work is that it indicates technical proficiency in this field. The work suggests that USSR scientists were aware of and were employing tissue culture technics, animal virus assay methods, and other standard procedures of Western laboratories.

Several papers of 1956 and 1957 reported the use of bacteriophage for the identification and typing of sensitive enteric bacteria, and the sequence of events following phage infection of bacteria (electron microscopic work). The papers indicated an understanding of the various stages of the infective process, and of quantitative phage technics, multiplicity of infection, host-range, mutual exclusion, plating efficiency on different media, and like phenomena. Unfortunately, few data were presented, but the citations and the papers themselves suggest that current concepts were known to the Soviet workers.

In a paper published in 1957, Tikhonenko reported on "morphological changes in the protoplast of the bacterial cell during phage lysis." The data consisted of electron microscope photographs, which were not of outstanding quality. Once again, the work emphasized that the "phage particle is represented by the protein macromolecule chain coiled into a ball, the free end of the chain being the tail of the phage particle." This emphasis on the importance of protein components rather than nucleic acid appeared to be a major difference between USSR and Western views on bacteriophage structure. The author claimed that infected protoplasts of *Bacillus mycoides* were transformed into phage particles and that various morphological stages in phage development could be seen. This was not evident from the photographs. Unfortunately, no information was provided on the method of preparing protoplasts, and there were no references to any studies on the subject of protoplasts or of cell wall formation in this paper.

In a series of papers by Zilber (1951–1956), it is possible to trace the progress of virus and phage work in the USSR. It is quite clear that studies in this area during 1951–1953 were naive and in no way comparable to contemporary investigations in Western laboratories. However, by 1953, there were indications (from Zilber's paper) that USSR ideas were changing. Zilber was against interpreting viruses as simply "filterable forms of bacteria." He felt that virus diseases were infectious and that the "spontaneous generation" of virus was open to question. His 1953 paper indicated familiarity with lysogenic phenomena, and he felt that these might explain some of the "filterable form" work.

By 1956, in a monograph entitled *The Study of Viruses*, Zilber, and undoubtedly other USSR investigators, had become familiar with much of the current Western literature in virology. This publication was a comprehensive discussion of work on animal, plant, and bacterial viruses, and covered studies in Western and USSR laboratories including such topics as virus morphology; inclusion bodies in virus infection; the chemical composition, concentration, and purification of viruses; culture methods; variability; interference; immunity; chemotherapy; bacteriophage methods; tumor viruses; the origin of viruses; viruses and the environment (host-virus interactions and physical and chemical agents); and the epidemiology and classification of viruses.

This monograph of Zilber's is of considerable importance, inasmuch as it indicates the manner in which a technically and conceptually weak area of research in the USSR could develop within a period of 3 to 4 years. (It is interesting to speculate as to whether the USSR scientific development in this area from 1950–1953 was really accurately portrayed by the published material.) At any rate, by 1956, the USSR interest in virology appeared to be burgeoning, and the potential for carrying out successful research in this area seemed to be increasing.

Although Zilber's monograph cited many USSR contributions in the field, it should be emphasized that the quantity of experimental data provided in many of the papers was limited. There were many discussions, citations of work done (in summary form), speculations, references to other USSR work, and so on. Yet much of the work appeared to lack scientific precision in terms of experimental protocol, methodology, and the recording of data. Detailed information as to how a particular experi-

ment was performed was usually lacking. For the most part it would be almost impossible for an investigator to repeat many of the experiments by relying solely on the information provided in the translated papers. This situation was observed repeatedly during this review of the USSR microbial genetic literature.

9. INDUSTRIAL ASPECTS AND METHODOLOGY

Several aspects of this research were influenced by USSR microbial genetic concepts. For the most part these were applied problems. A short summary of some of the research in this area may be helpful.

Abstracts covering the 1956–1957 period indicate Soviet interest in research on such problems as the increased production of citric acid by selected *Aspergillus* cultures; on culture methods for yeast and fungi; on fungal metabolism and its relation to antibiotic production; on milk pasteurization; on the preservation of microbial cultures; on the importance and use of bacteriophage in certain aspects of industrial microbiology, for example, in the preparation of cheese, beer and wine; and on spore formation and problems of food contamination in industry. (There was also evidence of interest in chromatographic procedures, electron microscopy, etc., as methods for general biological and biochemical investigation.)

In several papers writtin in 1952, problems relating to the principles of breeding microorganisms for industrial use were discussed. The selection of strains of microorganisms for certain purposes was emphasized, such as the economic value of yeasts with low fermentative activity for the production of non-alcoholic beverages. It is evident that the industrial work during this period was also influenced by Michurin-Lysenko biology with its motive of "the directed remodeling of nature".

Kvasnikov (1952) was critical of the pure culture methods used in industrial microbiology, since he felt that this neglected the importance of directed change in the hereditary properties of microbes. He suggested, for example, changing the biochemistry of the yeast cell by culturing it together with certain lactic acid bacteria to reduce the volatile acid-accumulating capacity of the yeast. No data were presented in this paper.

Ryabchenko (1952) reported on the continuous breeding of microorganisms in industry. He claimed that the method, introduced in 1950, was in harmony with Michurin's biological teaching on the "unity of the environment and the organism." By culturing microorganisms under laboratory conditions, the author felt that the cells were being subjected to environmental influences which caused changes in the properties of the organism. "These changes become hereditarily fixed and determine the character of further development. This can result in the loss of industrially valuable properties."

By employing continuous breeding methods, the author felt this could be avoided. This "continuous breeding," not to be confused with the Western chemostat or bactogen methods, involves "breeding under complex industrial conditions in which changes in the chemical composition of the medium take place not only as a result of the formation of grape sugar, as for example, in the wine-making industry, but also as a consequence of the formation of products from the exchange of substances by other microorganisms besides yeast that have entered the grape juice by various means. Under such conditions, stronger specimens of yeast of the improved breed may be developed which will successfully cope with the harmful influence of the increasing alcohol concentration and with the products of the life activities of competing species of microorganisms in the grape juice. The influence of competing species is known to be very important. Under inter-species conflict, depending upon the pecularities of the environment, individual specimens acquire properties which make them more adaptable in the ecological sense and more useful for industry."

It is evident from these papers that emphasis was placed on the inheritance of acquired characteristics. No data or experimental details were presented to support the contentions of these authors. On the basis of such papers, it seems that the research trends in the academic laboratories had considerable influence on the work carried on in industrial microbiology.

10. RADIATION BIOLOGY

Many of the aims of USSR work in radiation biology closely approximated Western interests in this area. Abstracts for the 1955–1957 period indicated concern over the problems and tasks of radiation genetics; the effects of ionizing radiation on human heredity; and problems of radiation-protection and the effects of radiation in altering

the hereditary traits of animals, plants, and microorganisms in a desirable fashion. Emphasis was still placed on the importance of experimental genetics as a basis for substantiating the philosophical theses of materialistic natural science. Demands were also made for a greater combined effort on the part of geneticists, microbiologists, cytologists, physicists, mathematicians, and chemists to study and solve problems in radiation genetics. Interest was noted in the effects of radiation on DNA and RNA synthesis and antibody formation, and in problems concerning health physics and medical radiology.

Several experimental and discussion papers covered the period 1952–1956. Aleksandov (1952) reported on the experimental analysis of susceptibility in which he studied the temperature-dependence of ultraviolet damage on paramecia. Measurements were made on motility and division time, but no biochemical work was attempted. Data were presented and the experimental details were given in more detail than is usually found in USSR papers. A comprehensive literature survey, including both USSR and Western research, was also presented.

Graevski (1953) studied the influence of oxygen on the damaging action of ionizing radiation. In these bacterial studies decreased radiation damage was found when oxygen was removed. Results similar to this have been reported by many Western investigators.

Discussion papers by several Soviet authors indicated considerable interest in the use of radioactive isotopes for biochemical studies, particularly in work on photosynthesis, nerve action, and oncology. Engelhardt (1955) gave interesting reasons for the emphasis on these areas of research. To understand the nature of photosynthesis, the author feels, would represent an understanding of a "process on which all life on earth depends—the photochemical utilization of radiant energy." Such progress would be "a step toward increasing the food resources of mankind and decreasing the threat of hunger and want." The motivation for the oncological research was equally humane, namely, relief from cancer, since "tumors are the most persistent and dreadful enemy of human health."

A paper by Alikhanian (1956) discussed the lethal and mutagenic effects of ultraviolet radiation on microorganisms. This paper presented a review of ultraviolet effects, the relationship between ultraviolet action spectra and nucleic acid absorption, and the various theories on the mechanism of action of ultraviolet irradiation. Alikhanian cited the work of Hollaender, Duggar, Lea, and others in this field. The application of the target theory of radiation injury was discussed, and the importance of the physiological state of the radiated cells (i.e., treatment before, during, and after radiation) was emphasized. The work of Kelner and of Kovalev (USSR) on photoreactivation was discussed. The effect of temperature and the relationships between radiation dose, lethality, and mutation frequency were also covered. The author concluded that the effects of ultraviolet irradiation were both direct and indirect. He proposed that initially the damage was at the level of DNA and RNA and that subsequently this damage was expressed through other biochemical manifestations.

Erokhina and Alikhanian (1956) reported on the influence of photoreactivation upon mutation in *Streptomyces griseus*. Since it was difficult to quantitate the increased formation of streptomycin, these authors measured the loss of streptomycin-forming capacity, that is, those colonies with *zero* streptomycin-forming activity. They employed an alternating series of ultraviolet treatments followed by photoreactivation, and in this manner they were able to detect the strong mutagenic action of large ultraviolet doses. Under these conditions they found a significant increase in the number of mutations that control streptomycin formation, whereas there appeared to be no increase in the number of streptomycinless mutants when only single ultraviolet exposures were used. However, these single doses were sufficiently high to increase the frequency of formation of morphological mutants. The authors cited Western research extensively and appeared to be familiar with current problems in radiation biology.

A paper on the effect of X-irradiation on the content of sulfhydryl groups in yeast was published by Galtsova (1955). She claimed that the number of free —SH groups were increased two to three times after pressed yeast was treated with 120,000–130,000 r of X-rays. While data were available to support these findings, she made several claims which were interesting but undocumented. Galtsova reported that this increase in —SH groups was retained in the progeny cells for 24–48 hours, the equivalent of 100 generations, and that this resulted in "deviations in structure and metabolism."

Some work by Meissel (1957) was of interest. There was a report on the use of chemical agents to "block the surface of mitochondria" and subsequently to increase the radiation-resistance of the cells. These studies were carried out as part of a program to investigate the physiological significance of intracellular structures. Meissel reported that although the fluorescent alkaloid berberine reduced the viability of yeast 40 per cent and also reduced respiration and oxidative phosphorylation, the surviving cells were radiation-resistant, as was their respiration and oxidative phosphorylation. The author stated that "substances which actively accumulate in mitochondria, viz., berberine, ethanol, and ether, raise the radiation-resistance of cells in terms of their viability, respiration, and oxidative phosphorylation." This he felt was due to a change in the physical-chemical properties of the mitochondrial surface. A similar effect was reported with agents which "block" the nucleus, but no effect of "blocking" the vacuoles was found. The presentation of data in this paper was poor. While the methods used to measure the effects of the treatment appeared to be reasonable, all the results were expressed as "percentage of control," and no actual figures were given for viability, or other parameters. Hence the evaluation of this work was difficult. The study was interesting but inconclusive in its reported form.

Meissel (1955) also reported some of the work of his group, on the "Biological Effect of Ionizing Radiations on Microorganisms," at the Geneva Conference on the Peaceful Uses of Atomic Energy. The paper discussed the direct injuries of the microbe protoplast; the morphology of "radiation disease" in microorganisms; biochemical changes in microbes as a result of irradiation, such as disintegration of phosphorus compounds, radiation influence on the rate of synthesis of phosphorus compounds in yeast organisms; or changes in the sterol metabolism of microorganisms under the influence of irradiation, and disturbances in vitamin metabolism in microorganisms following irradiation; functional changes of microorganisms under the influence of irradiation, as, for example, the interrelation between the intensity of irradiation and the degree of survival of microbes, correlated with changes in respiration, fermentation, and oxidative phosphorylation.

As a result of these studies, Meissel concluded that "these data open real perspectives for the deliberate alteration of the microorganism's metabolism not only by means of mutations, but also by exerting a radiation influence on the whole population of the microbes participating in the production process. It should be emphasized that the study of the morphology, physiology, and biochemistry of microbes both immediately after irradiation and in the process of radiation sickness that develops in them afterwards made it possible to reveal some of the most probable radiation-affected structures and chains of the metabolism, and to draw, to a first approximation, a general picture of disturbances taking place in the vital activity of a microbe cell as a whole organism caused by irradiation." This is an interesting discussion paper, but the limited data and paucity of experimental detail made it difficult to judge it as experimental work. Apparently Meissel has an active group, and it is to be assumed that detailed data are available to support the analysis and deductions.

In general, radiation biology seems to have been encouraged in the USSR, and microorganisms have been employed in such work quite extensively.

11. MISCELLANEOUS—GENERAL MICROBIOLOGY

Some miscellaneous material appeared to be of sufficient interest to warrant inclusion in the review even though it was not specifically concerned with microbial genetics. Abstracts covering the period 1955–1957 touch on such varied research as studies on the biological action of ultrasonics; the use of ultrasonics to prevent microbial spoilage of fruit juices; the distribution of bacteria in the soil of various regions of the USSR; marine microbiology and the problem of controlling bacterial growth on submerged parts of ships; the microbial flora of the ocean and its relation to such "physiological activity" as photosynthesis in certain ocean layers; the use of microorganisms for soil enrichment; and similar topics.

Many of these aspects of USSR microbiological work have need of methods and concepts developed in microbial genetic studies. Hence, to some extent, the screening of marine paints for their inhibitory effects on marine microorganisms has been concerned with problems of selection and resistance of microorganisms. Certainly, studies on the interrelationships of soil microorganisms must take into account the interaction between genotype and phenotype, induced enzyme formation, selection, symbiosis, and other problems related to the

genetics of microorganisms. It would seem reasonable to expect that the progress of Soviet microbial efforts in many diverse areas will very definitely be influenced by the calibre of the work now being carried out in USSR microbial genetic laboratories.

12. HISTORY AND IDEOLOGY

In this section an attempt will be made to review briefly the development of USSR microbial genetics since 1950 and to point out the extent to which political, philosophical, and ideological concepts have influenced USSR microbial genetic studies and the field of Soviet microbiology in general. In the previous sections, numerous references have been made to this aspect of the problem. Evidently a mixture of ideology and science has frequently caused severe repercussions in Soviet research laboratories, and this has been a major factor in preventing the more rapid progress of microbial genetics in the USSR. This lag was reflected in many areas of Soviet microbiology.

The slow development of USSR microbial genetics was directly related to the Soviet purge of animal and plant geneticists that began in the 1930's. By 1932, the All-Union Conference on Genetics had passed a resolution demanding that genetics "conform to the principles of dialectical materialism." The great Russian geneticist N. I Vavilov was eventually replaced by T. D. Lysenko, and in 1942 Vavilov died in disgrace. Lysenko, following the doctrine of Michurin, attacked the concepts of Mendel-Weismann-Morgan genetics and established the principle of the inheritance of acquired characteristics as *the* acceptable doctrine in Soviet genetics. The entire experimental basis of classical genetics was discredited and disregarded, geneticists were purged, and USSR progress in the field of genetics came to a halt. By 1948 Lysenko had been elected to the Presidium of the USSR Academy of Science and made Director of the Institute of Genetics.

During this period studies in the West on the genetics of *Neurospora* and yeast were progressing, and by the late 1940's the work on microbial biochemical genetics was already assuming considerable importance. In the early 1950's bacterial and bacteriophage genetics began their rapid development, aided tremendously by the active participation of physicists, chemists, and immunologists, together with the geneticists and microbiologists. It was in an atmosphere of suppression, ridicule, political pressure, and need for conformity that most of the USSR work in microbial genetics took place from the 1940's until the mid-1950's.

The vehemence of the "struggle between two world outlooks, materialism vs. idealism" was emphasized in discussion papers by Ivanov (1954) and Nuzhdin (1953). Ivanov's paper, entitled "How Studitskiy Fights Neo-Darwinism," illustrated the violent fight for survival between the anti- and the pro-Lysenkoists. (Studitskiy was a pro-Lysenkoist and a follower of Lepeshinskaya's teachings on non-cellular living matter; Nuzhdin was also pro-Lysenko.) These arguments were frequently pseudo-scientific. The degree of vituperation exhibited in them reflected the seriousness of the conflict and the threat to survival of the individual investigators. To be accused of practicing Mendel-Weismann-Morgan genetics was, in effect, to be accused of a political crime.

Michustin (1954) reported on the Sixth International Congress of Microbiology in Rome. Commenting on the lateness of arrival or the absence of representatives from a number of the People's Democracies, he said that they were delayed or unable to attend "notwithstanding the considerable efforts of a group of progressive Italian scientists, members of the organizing committee, to arrange for their visit." One entire page of his report was devoted to this "restrictive" aspect of the Congress. Comment was made on the travel restrictions for those attending the Congress (to 100 kilometers around Rome unless special permission was granted). Michustin lauded the Italian organizing committee for placing USSR chairmen on several sections. Concerning the scientific program, Michustin made the following comments: "Of 262 communications in general microbiology about 40 were on bacterial genetics. The Mendel-Morgan conception of heredity was dominant in the papers presented by the foreign scientists . . . . It must be noted that many of the papers read at the Congress were based on the unscientific conceptions of Weismann-Morganism. For example, they spoke of the 'recombination of genes' in bacteria during the sexual process, although the latter has yet to be proven by anyone. This unfounded speculative treatment of observed data gave the impression that a profound crisis is being experienced by Morganist genetics, especially in microbiology . . . . Thus at the Congress there predominated either communications on small, partial questions bearing a doubly empirical character,

or else reports built upon erroneous metaphysical postulates. It is of course true that the practical material of these communications was not infrequently of interest. In contrast, the reports of the Soviet delegation were of the nature of scientific theoretical generalizations, founded on the principles of Soviet materialistic biology. It is not surprising that they attracted the attention of the members of the Congress. The progressive elements among the foreign scientists strove to obtain guiding indications from the Soviet delegates, while other scientists tried to satisfy themselves clearly as to the theses of Soviet science, so that they could either accept them or raise their own objections to them, while still a third group of the scientists, hostile to materialism, plainly kept clear of all discussions." Michustin continued, "A substantial political result of the work of the Congress was the unanimous adoption, at its close, of a resolution calling on scientists to use the achievements of science for humane purposes, and to observe the Geneva Convention of 1925 on the prohibition of the use of bacteriological weapons."

A large part of this report on a scientific Conference was devoted to political and cultural aspects of the trip to Italy and the like. It is certainly clear that the USSR scientists in Russia would obtain very little if any information about the actual scientific proceedings of the Congress.

Troitskiy (1955), in a paper called "In Spite of the Scientific Truth," discussed the importance of the problem of the variability of microorganisms in industrial, agricultural, pharmaceutical, and medical studies. He severely criticized some of the USSR scientists for "introducing confusion" and "impeding the progressive movement of science." His statements on the research of Boshyan (see p. 56) were illuminating, since Boshyan's investigations followed the Michurin-Lysenko-Lepeshinskaya doctrines quite closely. "He [Boshyan] disoriented not only practical workers in microbiology, but broad masses of the public as well. A number of the principles advanced by him are in sharp conflict with data of modern science and practice. Such, for example, are his statements that filterable viruses and microbes are mutually capable of becoming converted from one to the other; that viruses and microbe forms change into crystals from which filterable viruses and microbes can again be obtained; that parasites and saprophytes change constantly from one to another; that filterable forms of microbes and viruses are bodies of one and the same order; and that immunity against any infection is a nonsterile infectious immunity." Troitskiy emphasized that "science needs facts." It is worth reflecting on how badly USSR work in microbial genetics needed such a creed during the early 1950's.

As Troitskiy reported, an investigation of the work of the Laboratory to Study Microbe Variability (headed by Boshyan) resulted in an official statement by a USSR microbial committee that the research had been "fruitless for medical science and practice and for solving theoretical problems of the variability of microorganisms." The laboratory was thereafter closed. Troitskiy ended his discussion with a frequently quoted reference to science and ideology, "Soviet microbiology and immunology will develop on the basis of advanced biology and physiology, and on the basis of Marxist methodology, using the richest scientific heritage. On this basis Soviet microbiologists will continue in the future to develop actively the problem of the variability of microorganisms."

In subsequent papers by Dubinin (1957), Kriviskiy (1957), and Nesmeyanov (1957), there seemed to be evidence of a de-emphasis upon Lysenkoism and a desire for a "scientific" science of genetics. Criticism was expressed at the way in which "deviationists" in science had been treated. Dubinin, who was one of the unfavored group during the period of strong Lysenkoism, now appeared to be regaining stature. While Dubinin's paper indicated familiarity with modern Western microbial genetics, he made every effort to cite and emphasize USSR work, such as the priority of the 1925 studies of Nadson and Filippov on the mutagenic action of ionizing radiation upon microorganisms and the use of radiation for the selection of high penicillin-producing strains of *Penicillium*. Emphasis was placed on the development of methods in the USSR and their utilization in the West. Dubinin stated that "these discoveries will soon be rightfully accepted as fundamental among the groundwork, based on natural history, of the Marxist philosophic materialism."

In short, it appears that genetic science and political ideology had not been separated even in 1957. However, to judge by the many references to Western work, the USSR scientists in considerable numbers are certainly becoming exposed to non-Soviet microbial genetic thought and technic. While the USSR geneticists are undoubtedly still paying lip service to USSR ideology, they cur-

rently appear to be scientifically more informed and outspoken than at any time since the rise of Lysenkoism. The importance of this shift in estimating certain trends in USSR microbial research will be discussed in the next section.

TRENDS IN USSR MICROBIOLOGICAL RESEARCH RELATING TO MICROBIAL GENETICS

In the course of discussing the work in the different areas of research, an effort was made to indicate possible trends in future USSR research, and to discuss the role of politics and ideology in shaping and influencing Soviet genetics. The material in this section will attempt to summarize these observations and to indicate, on the basis of reports by Soviet scientists, what appear to be the major USSR interests in microbial genetics.

It seems clear that the influence of Lysenko had diminished considerably by the mid-1950's, and that by this time some USSR scientists already appeared to have access to Western microbial genetic literature. While the quality of the Soviet research in this field still remained below average, the familiarity with current Western concepts and experiments had done much to encourage an increased demand for similar, extended USSR research plans. By 1957 a number of Soviet scientists were outspoken in demands for a serious and concentrated USSR effort in various aspects of microbiology related to microbial genetics.

As early as 1954, Soviet scientists were publicly suggesting that there be more contact, exchange of investigators, attendance at symposia, and so on between USSR and non-Soviet scientific circles. This demand remained evident in 1955–1956. In the USSR publications there were repeated requests for collaboration between microbiologists, geneticists, biochemists, physicists, and mathematicians in order to further the progress of microbial genetic research.

As to plans for future research, the statements of several Soviet authors are worth noting. By way of introduction, it should be remarked that a considerable amount of the work which has been reviewed here was either medically or pharmaceutically motivated. A great deal of the microbial work involved pathogenic microorganisms, their variability ("directed" or otherwise), and their control by various anti-microbial agents. Even most of the so-called "basic studies" employed pathogens or used microorganisms which were of industrial or pharmaceutical value. It would be foolish to ignore the USSR interest in research of very definite applied or practical importance.

In Dubinin's (1957) paper, a strong plea was made for greater emphasis on theoretical basic research and on its support by the USSR government. It was interesting to note a paper by Kalabukhov (1957) which was highly critical of work that did not take into account statistical variation in living organisms, and in which he called for greater attention to sound scientific data. Nesmeyanov (1957) reported on basic trends in the work of the USSR Academy of Sciences and emphasized the fact that microbial genetics and biochemical genetics were of sufficient importance to have been given high priority by the government. There were also indications in this report of a more liberal trend in Soviet science, a trend which may provide increased opportunity for progress in such research.

Krivisky (1957), in the Eighth All-Soviet Convention of Hygienists, Epidemiologists, Microbiologists, and Infectionists, emphasized the importance of microbial genetic investigations and the investigation of problems of chemical genetics. His report indicated familiarity with Western research in microbial genetics, and he asserted that "the expansion of investigations of bacterial genetics has become expedient." He revealed a general disenchantment with the Lysenko-Lepeshinskaya doctrines that had influenced USSR microbial genetics, and emphasized the need and desire to increase USSR research on the mechanism of drug resistance, and on the search for antiviral and anti-tumor agents. Krivisky commented on the unfortunate fact that so few papers in microbial genetics were given at the Convention, and pointed out the importance of the recognition of this work in medical circles, and specifically, the need for including such papers in medical conferences.

In a progress report by Engelhardt (1957) covering the work in the Department of Biological Science of the USSR in 1956, there were indications that the USSR biologists were emphasizing the following: continuous culture methods for growing microorganisms; radiation biology studies, radiation genetics, and the role of nucleic acids in the cell; advances in microbial genetics (mostly of an unspecified nature); and cell particles and biochemical activity and photosynthesis. Engelhardt felt that not enough work was being done in virology. He expressed concern with an "en-

gulfing of certain aspects of biological science by biochemistry and biophysics," and entered a plea for a greater exchange of information between USSR and non-Soviet scientists.

Certain general trends can be seen from the 1955–1957 abstracts of USSR research. There was still concern over the problem of Mendel-Morgan genetics vs. Michurin-Lysenkoism. There appeared to be an increased desire for greater international cooperation and the exchange of experiences as well as standardization of methods of research. Concern was expressed over the discarding of all Western genetic concepts as "formalistic," since, as was pointed out, "some aspects may prove useful." Emphasis was placed on "the widest utilization of new physical and chemical methods of research, and the rapid penetration into the physical-chemical essence of the elementary vital functions," such as the role of nucleic acids, the chemistry of mitosis, and the use of biochemical mutants. Once more it is to be emphasized that while references were made to such work as "currently progressing in USSR laboratories," no specific citations were given, and comparatively little work of this sort came to light during the preparation of this review.

It would appear that USSR microbial genetics is entering a period of "awakening" which may reflect some lessening of political pressure on the conduct of work in genetics itself. While the reports seen during this review were generally not of a very high scientific calibre, they did show progressive improvement during the 1950–1957 period. Since frequently there was a lag of several years between the time a research paper was submitted and the time it was published, it is possible that current USSR research is better in quality. It is certainly clear that a number of USSR scientists in the fields of microbiology, genetics, and biochemistry are anxious to promote microbial genetic research in the USSR. Assuming that this desire meets with official approval, USSR research in microbiology may favor microbial genetic aspects in the future.

THE USSR POTENTIAL FOR RESEARCH IN MICROBIOLOGY RELATING TO MICROBIAL GENETICS

Estimating the research potential in any field is always difficult, especially if the only contact one has had with the work is through translated journals and abstracts. Much importance should be attached to the calibre of the investigators, the laboratories, the students, the available financial support, and so forth. However, on the basis of the material covered in this review some observations on the USSR research potential in microbial genetics may be risked.

First, it is quite clear that the progress of science in Russia depends to a very great extent on the prevailing political climate. When Lysenkoism was the supported doctrine, genetics made little progress and even took several long steps backward. While there are still indications that USSR scientists must pay heed to certain basic Soviet doctrines, such as Michurin biology, it would seem that by 1956–1957 the Soviet scientists had access to Western literature and could express themselves with a reasonable degree of freedom.

The quality of the USSR research in microbial genetics had not attained a level comparable to Western work by 1957. Although aware of current concepts in the field, their experimental methods were lagging in certain areas, such as chemical genetics and bacterial and bacteriophage genetic technics. On the other hand, it was evident from the manner in which the USSR had mobilized research in such fields as that of antibiotic screening and production that they have the capacity to direct a major research effort to a certain area rapidly when this is desired.

Taking the expressed interests in microbial genetics at face value, one can imagine that financial aspects will not be the limiting factor in the success of the program. More important is the question of the calibre of the Soviet scientists working in this field, and this is most difficult to evaluate. There are certainly outstanding Soviet research men remaining in microbial, genetic, and biochemical research who were trained prior to the Lysenko period. The major problem may be the quality of the young Soviet scientists who have been schooled in the views of Michurin, Lysenko, Lepeshinskaya, and others, and who were first introduced to research through contact with experimental work having limited scientific merit.

If we assume that the Soviet scientific personnel are basically capable, and that the poor performance in past USSR research in microbial genetics represents work done under political and ideological pressures, then the potential for future successful work in this area should be good.

Finally, the most important factor in determining the success or failure of the current desire to

"develop USSR genetics along present-day scientific lines" is the extent to which scientific work remains free of political and ideological interference. There have been reports (January 1959-U.S. newspapers) that Lysenko has resumed power on the Soviet scientific scene, and has received backing from Khrushchev. If true, this may mean renewed emphasis on practical applied science, and the return of a political-scientific conflict in genetics. Should this occur, it is unlikely that the USSR will be capable of effective advancement in microbial genetics.

MICROBIOLOGICAL RESEARCH RELATING TO MICROBIAL GENETICS IN THE "PEOPLE'S DEMOCRACIES"

While this review is fundamentally concerned with Russian research, a number of references were available on studies carried out in Hungary, Poland, Czechoslovakia, China, and other Soviet allied countries. These were primarily abstracts covering the period 1955–1957. There was some indication that studies in bacterial and bacteriophage genetics and chemical genetics, for example, had developed much further in these countries than in Russia itself. This appeared to be particularly evident in several of the abstracts of Polish microbial genetic research where the studies approximated the character of contemporary Western work.

LIMITATIONS OF THE PRESENT REVIEW

In reading and interpreting this review, and in weighing the worth of the original reference material, one should be aware of several important limitations.

One cannot be absolutely certain that the body of material, and in particular the full-length manuscripts, formed a representative sample of the USSR research in microbial genetics during the period 1940–1957. For example, only a limited number of detailed experimental papers were included, and the evaluation of technical data was therefore based on a comparatively small sample. The question of the manner of selection of the reference material to be translated has some bearing on this problem of a representative sample. Do these papers give a true cross-section of the Soviet research output in microbial genetics? Does a shortage of reference material in a certain area of research truly reflect a lag in research, or is it an artifact of selection?

The accuracy of the translations was an extremely important factor since the reviewer was incapable of reading the original Russian papers. In several instances, for example, the legends and descriptive material for tables and figures were either absent or inadequate. Was this attributable to the translator, or was the paper originally published in that manner?

Lastly, there were several indications that the USSR journals were running one to two years behind in the publication of experimental results. A paper published in 1957 was likely to have been submitted in 1955–1956. Therefore, the evaluation did not take into account the actual research output of 1957–1958, and in the latter period more significant progress may have occurred than was evident from the earlier material.

CONCLUSION

There certainly appears to be a general lack of information among U.S. scientists regarding biological research in the USSR, including research in microbial genetics. This situation can be contrasted to that in France where Grabar (1958) on several occasions has reviewed certain aspects of USSR microbiological research.

It is to be hoped that this report will serve as a preliminary basis for a periodic review of the field of microbial genetics. While this could be accomplished with the help of the abstracting and translating services now available, future surveys would be greatly facilitated if a trained microbiologist with a thorough understanding of Russian could perform the task needed to keep English-speaking scientists abreast of developments in USSR microbial genetics.

The field of microbial genetics in Russia appears to be receiving considerable attention there at the present time. It would seem no more than prudent to follow its progress.

SUMMARY

Generally speaking, the research on *Mutation, Adaptation and Variation* (Section 1) was poor. Even as late as the mid 1950's scientists working in this area appeared to be under strong ideological influences, and the conflict between Michurin-Lysenko and Weismann-Morgan genetics was apparent. The majority of the papers placed in this section deal, in one way or another, with directed modification and the importance of the environment in heredity. Numerous papers relate

TABLE 1

Summary of the Number and the Distribution of References Used in the Review

Section	Year of Publication in Original Journal									
	to 1940	1941–1950	1951–1952	1953	1954	1955	1956	1957	1958	Totals
Section 1 (Mutation, Adaptation and Variation)										
A. Manuscripts (AIBS)	—	3	9	8	17[1]†	5	12	16	2	72
B.* USJPRS Abstracts	—	—	—	—	1[1]	1	26[3]	1	1	29
C.* Titles and/or brief abstracts (AIBS)	21	28	41	32	27	23	27	6	1	206
Section 2 (Chemistry of Inheritance)										
A. Manuscripts	—	1	—	4	—	—	4	3	—	12
B. USJPRS Abstracts	—	—	—	—	—	1	8[3]	—	—	9
C. Titles and/or brief abstracts	—	5	2	2	—	1	1[1]	—	1	12
Section 3 (Drug Resistance and Antibiosis)										
A. Manuscripts	1	—	3	—	1	4	4	17	1	31
B. USJPRS Abstracts	—	—	—	—	1	16[4]	45[3]	9	—	71
C. Titles and/or brief abstracts	1	5	2	—	—	—	2	10	—	20
Section 4 (Sexual Recombination)										
A. Manuscripts	—	—	—	—	—	—	—	1	—	1
B. USJPRS Abstracts	—	—	—	—	—	—	—	—	—	—
C. Titles and/or brief abstracts	1	2	1	—	—	—	1	—	—	5
Section 5 (Growth, Cell Division and Cell Theory)										
A. Manuscripts	—	2	12	6	5	3	2	2	—	32
B. USJPRS Abstracts	1	—	—	—	—	—	—	—	—	1
C. Titles and/or brief abstracts	7	7	4	5	4	3	1	—	—	31
Section 6 (Evolution and Ecology)										
A. Manuscripts	—	—	2	3	7	1	—	—	—	13
B. USJPRS Abstracts	—	—	—	—	3	2[1]	4	6	—	15
C. Titles and/or brief abstracts	—	1	4	3	4	—	2	—	—	14
Section 7 (Metabolism and Physiology)										
A. Manuscripts	—	6	3	—	3	—	2	3	—	17
B. USJPRS Abstracts	—	—	—	—	—	5[1]	11[2]	2[1]	—	18
C. Titles and/or brief abstracts	4	8	5	1	3	1	8	2	—	32
Section 8 (Host-parasite Relationship, Medical Microbiology, and Immunology)										
A. Manuscripts										
Bacteriophage	—	5	4	2	1	—	2	4	—	18
Animal + Plant Virus	1	1	5	5	2	1	3	—	—	18
Medical Microbiology and Immunology	—	—	1	1	—	—	2	2[1]	—	6
B. USJPRS Abstracts										
Bacteriophage	—	—	—	—	—	1	14[8]	6[3]	—	21
Animal + Plant Virus	—	—	—	—	—	—	15[3]	6[3]	—	21
Med. Micro. + Immun.	—	—	—	—	1[1]	9[3]	48[9]	5[1]	—	63

* Some of the manuscripts may have been tallied in parts B. and C. of each Section.

† Superscript number refers to the number of research publications from the "People's Democracies" which are included in that group of references.

Section	Year of Publication in Original Journal									
	to 1940	1941–1950	1951–1952	1953	1954	1955	1956	1957	1958	Totals
C. Titles and/or abstracts										
Bacteriophage	5	13	3	6	4	3	3	3	1	41
Animal + Plant Virus	6	1	10	7	2	3	2	—	—	31
Med. Micro. + Immun.	—	2	—	—	1	3	5	—	—	11
Section 9										
(Industrial Aspects + Methodology)										
A. Manuscripts	—	—	4	—	—	1	—	—	—	5
B. USJPRS Abstracts	—	—	—	—	—	—	9[a]	2	—	11
C. Titles and/or brief abstracts	1	1	2	2	1	3	3	1	—	14
Section 10										
(Radiation Biology)										
A. Manuscripts	—	2	3	1	—	6	7	1	—	20
B. USJPRS Abstracts	—	—	—	—	—	2	4	—	—	6
C. Titles and/or brief abstracts	4	3	3	2	—	3	2	1	—	18
Section 11										
(Miscellaneous General Microbiology)										
A. Manuscripts	—	2	3	—	1	—	6	—	—	12
B. USJPRS Abstracts	—	—	—	—	—	4	7	1	—	12
C. Titles and/or brief abstracts	3	4	2	1	—	2	3	—	—	15
Section 12										
(History and Ideology)										
A. Manuscripts	—	1	3	6	4	4	2	7	—	27
B. USJPRS Abstracts	—	—	—	1[b]	—	1[b]	8[a]	10[a]	—	20
C. Titles and/or brief abstracts	1	2	1	1	—	1	—	—	—	6

Gross Distribution of Evaluated Material

	USSR	Peoples Democracies
Total number of manuscripts (AIBS-discussion and experimental)	283	1
Total number of USJPRS abstracts evaluated	240	57
Total number of title or brief abstract references (AIBS) screened.	456	—
	—	—
Total for USSR	979	
Total for Peoples Democracies		58
Overall Material examined	1037	

to the conversion of one species of microorganism into another, and considerable interest centered on the pathogenic bacteria (*Salmonella*, *Shigella*, *Brucella*, *Pasteurella*, etc.), viruses, antibiotic-producing microorganisms, and yeasts and fungi of industrial importance. Experiments were designed to demonstrate the conversion, for example, of Bacterium A to Bacterium B, through the assimilation by A of the products of metabolism of B. For the most part these experiments lacked suitable controls or quantitative measurements. Less than half of the papers presented experimental data, and this was usually of the "plus" or "minus" (qualitative) variety. A major effort appeared to be directed toward disproof of the concepts of spontaneous, random mutation and subsequent selection.

The influence of the Lepeshinskaya "school" in regard to the origin of cells from non-cellular living matter has had a significant influence on USSR microbial research. Although by 1955 there were serious efforts by some Soviet biologists to question the experimental findings of the "anti-cell theory" group in Russia, many Soviet microbiologists

seemed to feel compelled to introduce the concept of "cells arising from noncellular living material" into their microbial studies. The literature was replete with references to "filterable forms of bacteria" as "stages in the development of bacteria," and to the "interconversion of viruses and bacteria." In the published material examined, there was no adequate *experimental* basis to support such claims.

Several papers indicated that Soviet microbiologists since 1954 have had moderate access to the Western literature of microbial genetic research. Studies on spontaneous and induced mutation, DNA transformations, transduction, sexual recombination in viruses, bacteria, yeasts and fungi, the concept of gene-enzyme relationships, and similar subjects, were familiar to them. Although differences in interpretation are evident, Soviet scientists were nevertheless aware of current Western experimentation and trends in microbial genetics (at least to 1955). While there were frequently allusions to Soviet work of comparable quality, in Soviet review articles, there was little indication of any actual experimental work (including data and results) in the area of mutation, adaptation, and variation to substantiate those claims. Nevertheless, there are undoubtedly many Soviet scientists at present who are familiar with current Western microbial genetic research and techniques. The support and encouragement of these investigators could lead to a rapid development of this field in the USSR.

USSR research on the Chemistry of Inheritance (Section 2) indicates an increased interest and development in the area of nucleic acid and protein studies related to genetic problems. In the early 1950's the influence of the Lepeshinskaya group was still strong, and emphasis was placed on protein as the important factor in heredity, in such statements as that "cells which originate from protein then develop a nucleus." Here again no data were provided. By 1956, however, it appears that the full genetic importance of DNA had been recognized, and that the Soviet scientists interested in this work were aware of many of the current chemical genetic techniques. Most of the papers in this category were general discussions and covered the problems of the nature of the gene, gene action, virus reconstitution from nucleic acid and protein, and similar questions. There were several instances in which biochemical studies on nucleic acid base ratios, content in the cell, etc., were presented, and here (in contrast to the experimental work in the foregoing section) the methods and data appear to be reliable. From all of the work reviewed, it would seem that the calibre of the biochemical studies (applied to microbial genetics) was generally much higher than the microbiological aspects. There was evidence, first appearing in 1957, that studies were just beginning in the field of biochemical genetics, and that microbial nutritional mutants were finally being used to study problems in metabolism, enzyme formation, and the like. Hence, the lag in this area of research appears to be considerable. It should be emphasized that there seem to be several competent investigators engaged in this work. With access to the Western literature, and with freedom to pursue their investigations, reasonable progress may be expected in these chemical genetic studies.

In the area of Drug Resistance and Antibiosis (Section 3), numerous papers attempted to characterize the biochemical changes occurring in microorganisms and accompanying the development of drug resistance. Major emphasis was placed on the clinical importance of this problem. The search for new antibiotics occupied a large part of the research in this area. Particular emphasis was placed on the problem of anti-viral and anti-cancer agents by testing both synthetic organic compounds and biological products. Some of the principles and techniques of biochemical genetics were employed to screen for antibiotics that would inhibit the growth of cancer cells having metabolic deficiencies similar to those occurring in certain microbial mutants. Actinomycetes were used for the production of anti-viral agents which were tested on tobacco mosaic virus and bacteriophage. The names of many "new antibiotics" were evident, but the reported results (as well as the statements of several Soviet scientists) indicate that truly effective anti-viral or anti-tumor antibiotics were still lacking at the time. While some therapeutic effects were noted, it was apparent that much more work is needed in this field.

Studies on the mechanism of action of antibiotics on pathogens, on the means of combating therapeutic problems of drug resistance by using several antibiotics simultaneously, on the difficulties of extrapolating from systems in vitro to those in vivo, on increasing the production of antibiotics through an understanding of the cytological and biochemical changes occurring in actinomycetes during antibiotic production, and the like, pointed toward

a major USSR commitment in personnel, equipment, and funds for research in this field. Once again, there was a shortage or absence of experimental evidence in many of the reports of investigations. In those cases where biochemical properties were being studied, the reported methods and results again appeared more reliable than the microbial work.

As late as 1956 Michurin concepts still had a strong influence in this area, and the conflict between the concept of spontaneous mutation and selection as cause vs. that of directed modification by the antibiotic was very evident. Generally speaking, the source material in this area of research supported the view that Michurin biology has been a dominant feature in USSR biological research, but that interesting work was going on in this area which either paid only lip service to ideological dogma or avoided mentioning it altogether. Certainly, great interest does exist in the USSR in the problem of drug resistance and antibiosis. Although a large body of research was at the applied level, there were studies in progress at the basic level as well. Unfortunately, many of the papers that were supplied were difficult to evaluate, since the results were not quantitated, and many of the conclusions were unsupported by the evidence which was presented. There seemed to be some familiarity with work in other lands, but the major literature citations appeared to be based on studies done in the USSR.

There was little evidence of any extensive studies on Sexual Recombination (Section 4) in microorganisms. Some work was being carried on with actinomycetes using biochemical mutants, but the main emphasis appeared to be at the applied level, i.e., "vegetative hybridization" to improve industrial yeasts, antibiotic producers, etc. Confusion was still evident in the literature concerning the difference between heterocaryosis and true diploidization and segregation. There seemed to be little experimental interest in bacterial and viral recombination; and certainly there was no evidence of any work like the recombination studies of the Lederbergs, Jacob and Wollman, Hershey, Doermann, and others in Western laboratories. It was clear, nevertheless, from a number of review articles written by Soviet scientists, that the USSR investigators had read some of the literature on sex in bacteria and viruses, and were conversant with Western work in this area up to about 1955.

The USSR studies in the area of Growth, Cell Division, and Cell Theory (Section 5) were perhaps the most subject to political and ideological pressure. The source material clearly indicated the extent to which ideologically motivated concepts had influenced basic research. Until about 1955 O. B. Lepeshinskaya's doctrine on the "origin of cells from noncellular living matter, and the role of living matter in the organism" was a dominating factor in Soviet biology, including microbial genetics. There was a major area of research devoted to the "phase development of microbes", and the ontogenesis of individual bacteria. There were numerous reports on the regeneration of "filterable forms" of bacteria, and the "interconversion of bacteria and viruses". Particular attention was paid in all of this work to the pathogenic microorganisms. There were repeated references to the "regeneration of filterable forms of bacteria", and to the "modification of the nature of living organisms through controlled action and the action of environment". There were claims for "remarkable achievements in medical, veterinary, agricultural and industrial microbiology, in plant culture and in fruit growing". The impact of the "anti-cell theory" doctrine on microbial work was considerable. Occasionally, even in the early 1950's, one or two questioning papers were found, but it was not until 1955 that the first major criticism of Lepeshinskaya's experiments, based on their lack of scientific merit, was made public. Since that time there has been a noticeable decline in Lepeshinskaya's influence on theories regarding the origin of bacteria and viruses, changes in virulence, etc. In all of the source material seen in this area of research, either no data were presented or the claims for the regeneration of filterable forms of bacteria, virus and bacterial interconversion, etc. were based on inadequate experiments, i.e., were devoid of controls for contamination, mixed cultures, latent viruses, etc. Significantly, the references to work in this area (Section 5) are almost exclusively USSR literature citations.

Some effort in USSR microbial research appears to be devoted to the problem of Evolution and Ecology (Section 6) and the formation of microbiological species. Inherent in this area of investigation was the basic conflict between the pro-Lysenkoists and anti-Lysenkoists. In the early 1950's there was strong feeling in favor of the Lysenko concept of "the generation of one species by another". This outgrowth of Lysenko's plant work was soon evidenced in microbiological work

by the experiments on "filterable forms of bacteria" and their regeneration, under environmental influence, into new bacterial species. In none of these papers were any data supporting such proposals ever provided. This was the case even in those papers where Western work on recombination between *Salmonella* and *E. coli*, transformation and transduction, lysogeny and lysogenic-toxogenic conversions, etc. were cited.

The USSR investigators of the early 1950's who were working in this area (filterable forms, etc.) emphasized the role of an altered environment in causing a directed hereditary modification, i.e., the inheritance of acquired characters leading to the formation of new species. It was clear that USSR microbial genetics had been subjected to the same nonscientific pressures as animal and plant genetics. In 1954, there was some evidence that the anti-Lysenkoists were speaking out in favor of natural selection as a major factor in species formation. As late as 1956, Lysenko still maintained that new species were not the result of hybridization, but resulted from the generation of one species by another. Hence this entire conflict, so fraught with violence, vituperation, the lack of scientific method, etc., has had a very great influence on the progress of basic and applied microbiology in the USSR. The supposition that one species of microorganism can be experimentally converted into another by regeneration from filterable forms received its major support in the USSR on ideological and political grounds. In none of the papers covered in the preparation of this review was there adequate scientific evidence to support such a proposal. Research during the period 1955–1956 indicated an increasing awareness by Soviet scientists of the genetic importance of DNA and the current Western concepts of the theory of gene structure, gene function, and evolution, of the role of environment in controlling the phenotype, etc. One wonders how closely this trend may have been related to the decline of Lysenko's influence politically and scientifically, and whether following recent reports of Lysenko's resurgence one may anticipate an early termination of the progress and development of USSR microbial genetics.

While the majority of the papers in the area of Metabolism and Physiology (Section 7) were not directly concerned with microbial genetic studies as such, there were several reasons for including some of that work in this review. First, several of the reports concerned studies on microbial DNA, adaptive enzyme formation, pure culture technics, etc.; and second, a review of material in the general area of metabolism and physiology offered a means of comparing methods, collection of data, etc., in a related area of microbial research. It was of interest that ideological pressures were not apparent in this work. Generally speaking, the experimental approach to problems such as the effect of oxygen on the DNA of actinomycetes, the microbiology of cellulose, energy metabolism in heterotrophic bacteria, problems of the dynamic state of proteins and protein synthesis, etc. was reasonable. While the data were at times inadequate to support some of the conclusions, the quality of the research was better than in the strictly "genetic" papers. The biochemical work was satisfactory, and some knowledge of Western work in the field was apparent, i.e., aspects of in vitro protein synthesis and the problem of turnover, enzymes in the pentose cycle, etc. USSR studies on adaptive (induced) enzyme formation appeared to be in a rather primitive state, both technically and conceptually. There did not seem to be any indication that this important area of research was being investigated to a significant extent, except where it pertained to applied microbiology, i.e., fermentations, antibiotic production, etc.

The work discussed under Host-Parasite Relationships, Medical Microbiology, and Immunology (Section 8) covered bacteriophage studies, investigations on plant and animal viruses and pathogenic bacteria, preparations of vaccines, and views on immunity. In the early 1950's this area appeared to be subject to the same political-ideological influence noted in most of the microbial genetic work, i.e., there were reports of the interconversion of viruses and bacteria and their conversion to crystalline forms, the conversion of pathogens to non-pathogens, and vice versa by regeneration from filterable forms, the idea of nonsterile infectious immunity, i.e., "microbes don't disappear, but are transformed to virus or phagic forms which are inactive and cause no infection," etc. Such investigations were strongly influenced by both Lysenko's and Lepeshinskaya's teaching. No adequate experimental evidence was presented to substantiate the claims made in these studies. However, during 1955–1956, these investigations were severely criticized on technical, conceptual, and personal grounds. Many of the experiments could not be repeated, and the evidence obtained from electron microscope studies was easily reinterpreted along more orthodox lines.

It is noteworthy that by 1955–1956 much of the

Western work on quantitative bacteriophage techniques, the sequence of events in phage infection, phage recombination, the biochemistry of phage infection, the study of plant and animal viruses, i.e., tobacco mosaic virus reconstitution from RNA and protein, the crystallization of polio virus, methods of studying animal viruses using quantitative methods, etc., had become known to USSR scientists in this field. In 1956, this information was published in book form in Russia, an indication of the manner in which scientific material can be disbributed in the USSR under favorable conditions. One can speculate on the relationship between the appearance of this information in Russia, the interest it evoked among Soviet scientists, and the frequent references made by USSR scientists to Russian work of a comparable nature. However, very few such USSR experimental papers were seen during this review. For the most part, it would be difficult if not impossible for an investigator to duplicate many of the experiments, since the information provided by the Soviet authors is characteristically inadequate.

There was undoubtedly great interest in virus work from the biological, medical, and epidemiological viewpoints. It was clear, from statements in a number of papers that discussed the "Goals of USSR Microbial Research", that considerable emphasis will be placed on virus research in the future.

A number of aspects of research in Industrial Microbiology and Methodology (Section 9) were of interest. It was apparent that in the early 1950's Michurin-Lysenko teachings had influenced industrial as well as basic research. For example, papers on the principles of breeding microorganisms for industry emphasized the importance of the "directed remodeling of nature" and criticized the use of pure culture methods, i.e., desirable changes in the biochemistry of yeast could be brought about by culturing them with certain lactic acid bacteria. In using mixed cultures for various industrial processes, such as wine-making, it was proposed that "under inter-species conflict, individual specimens acquire properties which make them more adaptable in the ecological sense and more useful in industry." This, it was felt by the Soviet investigators, emphasized the importance of the inheritance of acquired characteristics.

Other aspects of industrial research related to microbial genetics were noted in references to studies on increased citric acid production by variants of *Aspergillus*; the survival of *Mycobacteria* and *Brucella* after pasteurization of milk; the preservation of microbial cultures; the relationship between bacteriophage infection and the souring of beer, etc. It appeared that the trends in industrial microbiology in the USSR reflected to a large extent the progress and the ideas prevalent in the basic research laboratories engaged in microbial work. This relationship would seem to hold serious drawbacks for those industries dependent on well-founded basic genetic experimentation.

Studies in Radiation Biology (Section 10) from 1952 to 1956 indicated that USSR workers in this field were thoroughly familiar with the Western literature on such topics as: the effects of ultraviolet irradiation on microorganisms; the target theory; UV dosage effects on survival and mutation frequency; photoreactivation; etc. There appeared to be widespread interest in the use of radioactive isotopes for studies of photosynthesis, for work on the chemical basis of nerve action, and for research in the field of oncology. It was not unreasonable to expect that isotopes will soon be employed on a wider scale in Soviet microbial genetic studies, i.e., in biochemical genetics. Such studies as those on the biological effects of ionizing radiation, on the mechanism of action of radiation, on the influence of oxygen, temperature, and other agents on the damaging action of radiation, on radiation effects on heredity, and on the need for radiation protection methods alike indicated considerable USSR interest in radiobiology and in the frequent use of microorganisms as the biological material of choice. It was interesting to note the frequent similarity in Western and USSR research aims in this area.

A number of research areas of interest were combined under the heading Miscellaneous—General Microbiology (Section 12). From 1952–1956 there was great interest in the use of ultrasonics for disrupting microbial cells and viruses, and the mechanisms involved, for biochemical and immunological studies, and for industrial purposes. Ultrasonics were used therapeutically with uncertain results, and were employed, again with uncertain results, for the production of vaccines. There was a strong interest in soil microbiology in various areas of the USSR; in the use of *Azotobacter* for nitrogen enrichment of composts; in the development of toxic paints which would resist marine bacterial growth; in marine microbiology and the relationship of the nature and density of the marine microorganisms to the physiological activity of certain ocean layers, etc.

Hence, while not directly related to microbial genetic work, it can readily be seen that all of these problems in some way might profitably draw on methods, concepts, and approaches currently available in microbial genetics. A strong USSR microbial genetics program would undoubtedly benefit many areas of Soviet microbiology and such related areas as tissue culture research. It would indeed be surprising if USSR scientists did not also realize this.

In any discussion of USSR research involving genetics, one cannot omit History and Ideology (Section 11). As already emphasized several times, USSR research in microbial genetics during the early 1950's appeared thoroughly dominated by Lysenkoism and Lepeshinskayism. The effect was chaotic. By 1953–1954 there were occasional papers which were critical of this unscientific research, and which directly attacked pro-Lysenkoists for "introducing confusion and falsehood and for impeding the progressive movement of science." As late as 1954, however, a USSR report of the Sixth International Congress of Microbiology in Rome dismissed all the Western microbial genetics papers by simply stating that the "Mendel-Morgan conception of heredity was dominant in papers presented by the non-Soviet scientists." By 1957, the picture had changed and several reports indicated genuine familiarity with Western microbial genetic work. In the 1957 report of the USSR Academy of Sciences, it was reported that microbial and biochemical genetics has been given a high priority by the Communist Party. This was accompanied by criticism of past behavior toward "deviationists," which suggested that there may be a more liberal trend in Soviet science, and an increased support of basic research. It is worth noting that recent reports of Lysenko's reappearance on the USSR scientific scene could have serious scientific consequences, even to the extent of preventing a possible "modernization" of the USSR genetics program. At present, Soviet microbial genetics appears to be at least five years behind the West experimentally. Conceptually, depending on how widespread is the distribution of Western literature, there is not so big a gap. If a liberal scientific policy is maintained in Russia, Soviet scientists should be capable of making considerable strides in the field of microbial genetics within a few years.

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LIST OF LITERATURE

[In the following list, only the beginning page of each cited reference is given, and for some items the reference is even more incomplete. The author of the review and the editors deeply regret this fact, but the translated materials were supplied without complete references and it would have taken great labor and would have involved an almost indefinite postponement of the publication of the review, probably beyond the period of its greatest usefulness, had there been insistence upon completeness of the references. We sincerely hope that from the information given readers will be able to find the original papers cited, and we emphasize that this departure from good editorial practice is not to be taken as a precedent. Ed.]

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NEW BIOLOGICAL BOOKS

The aim of this department is to give the reader brief indications of the character, the content, and the value of new books in the various fields of Biology. In addition there will occasionally appear one longer critical review of a book of special significance. Authors and publishers of biological books should bear in mind that THE QUARTERLY REVIEW OF BIOLOGY *can notice in this department only such books as come to the office of the editor. The absence of a book, therefore, from the following and subsequent lists only means that we have not received it. All material for notice in this department should be addressed to H. B. Glass, Editor of* THE QUARTERLY REVIEW OF BIOLOGY, *Department of Biology, The Johns Hopkins University, Baltimore 18, Maryland, U. S. A.*

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BIOLOGY: HISTORY AND BIOGRAPHY

GESCHICHTE DER ZOOLOGIE UND DER ZOOLOGISCHEN ANSTALTEN IN JENA 1779–1919.

By Georg Uschmann. Gustav Fischer Verlag, Jena. DM 33.25. xvi + 249 pp.; ill. 1959.

This is an exhaustive, scholarly, well-documented history covering the development of the zoological collections, museums, and institutes, and of zoological teaching and thought, at Jena. It begins with the year when Carl August, with the cooperation of Goethe and J. C. Loder, established his museum by purchasing the collections of Johann Ernst Immanuel Walch, Professor eloquentiae et poesis. It ends in 1919, the year when Haeckel died. While two short preliminary chapters deal with the period before Haeckel's advent in Jena (1861), the main text, like zoology in Jena itself, is dominated by Haeckel.

The book is based on a study of unpublished archival collections: university records, letters, and other documents. The illustrations include many new portraits, facsimiles of letters, diplomas, sketches, building plans, and so forth. Almost everything in the book is new; the author has deliberately repeated as little as possible of what has already been published by others. His contribution, therefore, is a supplement to, and not a substitute for, our existing knowledge of the great figures of Jena. It is of consummate interest as a further illumination of the character, ideas, and actions of Haeckel; but also of importance for the light it sheds on many others: Gegenbaur, Anton Dohrn, Strasburger, the Hertwigs, Schwalbe, Lang, Semon, Kükenthal, Ziegler, Roux, Driesch, and many others. Zoologists of the twentieth century have received a large heritage from their intellectual forebears of Jena, and Uschmann helps them in this book to take its measure.

JANE OPPENHEIMER

SIR RICHARD GREGORY. *His Life and Work.*

By W. H. G. Armytage. Macmillan & Company, London; [St. Martin's Press, New York.] $5.00. vii + 241 pp. + 1 pl. 1957.

For more than twenty years, Sir Richard Gregory served as Editor of *Nature*. During that time he made it what it still is today, the best known and most authoritative English-language journal of science in the world.

Richard Gregory was born on January 29, 1864, the son of a versifying shoemaker, in Bristol, England. He was brought up and received his early education during a time when the Labour Movement was beginning to attract attention in England. Thus, quite early was molded his "social consciousness," which was so much in evidence during his career as an interpreter and statesman of science.

At 19, after an apprenticeship as a shoemaker, young Gregory entered the Royal College of Science. Here he met H. G. Wells and formed a life-long friendship. Each had a profound influence on the other. Financial stringency forced Gregory to look for ways to increase his income, and soon he was writing scientific textbooks and teaching.

He began his scientific career at an auspicious time, in the last quarter of the 19th century, when popular scientific education (i.e. for the masses) was indeed popular. In 1893, Sir Norman Lockyer, then editor, appointed Richard Gregory to the staff of *Nature*. Thus began an association which lasted for almost a half century. During this time, Gregory surveyed the progress of modern science. As one of the editors and then The Editor, of *Nature*, in whose pages were reported the scientific advances of the first half of the twentieth century, one might say of Gregory that he rode the wave of future. In truth, he not only rode it—he helped to make it. His birth in 1864 made the world richer, his death in 1952 left it poorer.

This biography was written by his close friend, W. H. G. Armytage, who is Professor of Education at the University of Sheffield. It is based upon letters, notes, and other documents made available to the author by Sir Richard's widow. While this is an adequate sketch of a great man's life, his autobiography is written largely in the pages of *Nature* itself.

MORRIS C. LEIKIND

A WAY OF LIFE AND SELECTED WRITINGS OF SIR WILLIAM OSLER. *12 July 1849 to 29 December 1919. Introduction by G. L. Keynes. Dover Publications, New York.* $1.50 (paper). xx + 278 pp.; ill. 1959.

In 1931, when Henry Sigerist wrote a biographical history of medicine entitled *Great Doctors*, he discussed 57 physicians, the last of whom was Max Pettenkofer. In 1933, when he prepared a second edition, he added a new final chapter on William Osler. Few who were sensitive to movements in medicine during the early part of this century would doubt that Osler was a great force in American medical progress, both through his professional accomplishments and through the warmth and wisdom of his exceptional personality. Yet now, a half century after his death, excellent young men can graduate from excellent old medical schools and not know his name. "The publication of his textbook," wrote Geoffrey Keynes in 1950, in the introduction to the original edition of the present selections, "... ensured him immortality as a medical writer." But his immortality has been short-lived, and the iniquity of oblivion has too soon scattered her poppies over his memory.

It is to be hoped that the republication by Dover Publications of a group of Osler's writings, originally published by Oxford University Press in 1951 under the title *Selected Writings of Sir William Osler*, will win the acceptance it deserves. The selections were chosen as a centenary tribute to Osler by a committee of the Osler Club of London, assisted by Osler's nephew, the late W. W. Francis. They include 16 essays, on books and on men, on history and on medicine. The knowledge in them is sure, the wisdom deep, and the writing full of grace and wit. A half century after Osler's death, men of medicine, of literature, and of humanity may well remind themselves, by reading or rereading these essays, of the magnitude of their debt to Osler. This readily available volume may help them pay their equally pressing debt to the future by staying the hand of oblivion.

JANE OPPENHEIMER

DARWIN'S NOTEBOOKS ON TRANSMUTATION OF SPECIES. PART 1. FIRST NOTEBOOK (JULY 1837–FEBRUARY 1838). *Bull. Brit. Mus. (nat. Hist.), Vol. 2, No. 2. Edited with an introduction and notes by Sir Gavin de Beer. British Museum (Natural History), London.* £1 (paper). iv + pp. 25–73; ill. 1960.

ECOLOGY AND NATURAL HISTORY

TREATISE ON MARINE ECOLOGY AND PALEOECOLOGY. *Volume 1, Ecology; Volume 2, Paleoecology. The Geological Society of America, Memoir 67; prepared under the direction of a Committee of the Division of Earth Sciences, National Research Council, National Academy of Sciences. Vol. 1 edited by Joel Hedgpeth; Vol. 2 edited by Harry S. Ladd. The Geological Society of America, New York.* $22.50 (2 vols.). (Vol. 1) x + 1296 pp. + 3 folded maps; ill.; (Vol. 2). xii + 1077 pp. + 12 folded maps; ill. 1957.

These volumes are an outgrowth of more than 15 years of dedicated work. The purpose of the Committee and of the *Treatise* has been to evaluate marine ecology as it is used in the interpretation of the geological record.

The first volume summarizes those aspects of marine ecology most critical to geology. Twenty-nine chapters take up specific facets of the problem. These are written individually by appropriate specialists, the majority of whom have not been members of the National Research Council committees. Some chapters are devoted to particular properties of the marine environment. These include discussions of sunlight, salinity, temperature, oxygen, carbonates and carbon dioxide, nutrient elements,

trace metals, and particulate organic detritus. Others take up the ecological relations of specific environments: rocky intertidal surfaces, sandy beaches, coral reefs, estuaries and lagoons, level bottoms away from shore, and the deep sea. In addition, several miscellaneous but highly important problems are taken up separately: biogeography, commensalism, parasitism, symbiosis, plankton, lunar periodicity, fluctuations in littoral populations, mass mortality, and submarine canyons. Finally, a few geographical areas that have received intensive study are reviewed. These include the Baltic Sea, Black Sea and Sea of Azov, and the Caspian and Aral Seas.

The coverage of marine ecology in this volume is naturally somewhat spotty and uneven because of the personal interests of those involved and as a reflection of current trends and emphases in the field. Noticeably lacking, for example, are discussions of the role of genetic factors in animal ecology. This volume serves, nonetheless, as an invaluable synthesis of an extremely complex subject.

Nearly 300 pages at the end of Volume 1 are devoted to a series of carefully annotated bibliographies, each concerned with the ecology of a different group of marine organisms (principally those contributing to the fossil record). Some of the bibliographies are rather unsatisfactory because they were compiled many years before final publication, and many are incomplete because of reflecting the personal leanings of their authors. The bibliographies remain, however, a valuable addition to the *Treatise*.

The second volume follows much the same scheme as the first: a few introductory chapters, followed by a series of chapters of synthesis and analysis, and concluded by annotated bibliographies. This volume is really an attempt to test the usefulness of the principles set forth in Volume 1, as applied to the fossil record. Most of the paleoecological chapters report the results of long-term studies of specific geologic situations. The attempt has been made to include one such study from each major period in geologic history. The majority of these are digests of material published elsewhere.

If this second volume of the *Treatise* is looked upon as a statement of the present stage of development of paleoecology, the impressions are, with notable exceptions, a bit discouraging. The reader often has the impression after reading one of these detailed studies that he has been firmly convinced that the sky was blue or that water ran downhill during a given period in earth history. He is sure of little else. If this is a just criticism of the geological parts of the *Treatise*, the fault is not that of the editors or contributors, but rather of the limitations of the geologic record and the inherent difficulties in our interpretations of it. Perhaps the *Treatise* will serve indirectly to emphasize the weaknesses in the paleoecological method and thereby serve to stimulate research aimed at eliminating these weaknesses.

DAVID M. RAUP

POPULATION STUDIES: ANIMAL ECOLOGY AND DEMOGRAPHY. *Cold Spring Harbor Symposia on Quantitative Biology. Volume XXII.*

The Biological Laboratory, Cold Spring Harbor. $8.00. xiv + 437 pp. + 2 pl.; text ill. 1957.

The purpose of this symposium was to gather those interested in population change—human and otherwise—to exchange views. The composition of the participants, 17 speakers primarily interested in human populations and 20 primarily interested in other organisms, sheds some light on the symposium.

There seemed to be very little exchange of views between (human) demographers and those interested in general animal populations. While it is clear from the start that human populations offer a fearfully complex problem, the general lack of results on human populations is disappointing. L. C. Cole's introductory paper (one of the most interesting in the series) presents nearly as many interesting demographic ideas as all of the demographers together. In fact, the demographers seemed unaware of such important conceptual advances as R. A. Fisher's introduction of the "reproductive value" of a population, and no theory essentially newer than Lotka's early researches was made use of. Perhaps the very failure of demographers to make simplifying generalizations is the most useful conclusion to this section of the symposium. Science usually progresses faster when theory is able to keep abreast of facts; when the array of facts is as complicated as human demography already is, one despairs of finding a theorist who can set up a complete, adequate theory. It may be very true that demographers know too much.

The animal population workers were roughly divided into two schools over their views on density dependence. A. J. Nicholson (and, implicitly, F. A. Pitelka, H. N. Kluijver and others), supporting density-dependent regulations, maintained that a population is more likely to increase when rare and to decrease when common relative to some critical density. Their analysis was partly logical and partly empirical; the exact nature of the cause of increase and decrease is usually obscure. H. G. Andrewartha, L. C. Birch, A. Milne, and others, arguing completely empirically, said there was little evidence of specific density-dependent events, and claimed that another model was more realistic.

Perhaps the biggest achievement of the symposium was to have these views aired. While few of

the participants said anything unexpected, the questioning at the end of the sessions, coupled with papers such as T. B. Reynoldson's, revealed that both mechanisms are consistent with one another in most ways. Although the participants may have left in a turmoil, the reader may synthesize the views as follows. Let us say that dispersal is important to a species if its dispersal ability is small compared to the distance between nesting sites, food sources, and the like. Similarly, let us say that weather is important if the variation (i.e., unpredictability) in the weather's effect on the species is large during an animal's lifetime.

H. G. Andrewartha and L. C. Birch considered only populations for which dispersal and weather were important; the importance of these, combined with the species' capacity to increase, could obviously obscure density-dependent effects. A. J. Nicholson and others discussed situations (especially prevalent in the vertebrates) in which dispersal is great compared to the patchiness of the local environment and in which weather is unimportant. For these species, naturally enough, an equilibrium model, with true regulation, seems feasible. So far, there is no inconsistency in the two views. The only real difference lies in whether exterminations do take place with the frequency H. G. Andrewartha and L. C. Birch suggest, or whether a density-dependent regulation reduces the number of local exterminations. On this question there are insufficient data, and an almost religious fervor replaces objectivity in the symposium. The comments following some of the presentations make very exciting reading.

One further general conclusion of the symposium is worth mentioning. While it may easily be concluded that many species have density-dependent regulation, it is not always easy to see exactly what is happening. The biggest difficulty seems to be in properly interpreting the word density. Various papers bear witness to the fact that the most meaningful density is not just the number of organisms per unit of area. A new definition, involving the configuration of the habitat and, perhaps, the nature of the meetings which take place between organisms, would doubtless throw much light on population regulation.

There is not space to give adequate mention of the papers on subjects such as community structure and evolution theory. Although these topics are very important, they might better have been omitted from this symposium. For by the very nature of a symposium, unless the speakers have important new work to describe, a representative collection of speakers should be assembled to compare views on a whole subject. Few new facts emerged from this symposium, and most papers were slight modifications of data already familiar to population people. Although the publication of the symposium surely serves a useful purpose at present, I predict that it will be forgotten shortly.

ROBERT H. MACARTHUR

INSECT LIFE AND INSECT NATURAL HISTORY. (*Formerly Entitled: General Entomology*). *Second Edition.*

By S. W. Frost. Dover Publications, New York. $2.25. (paper). x + 524 pp.; ill. 1959.

This volume is said to be a revised (1959) edition of the 1942 issue entitled *General Entomology*. Without a copy of the earlier work and with no aid from the publisher or the author, it is difficult to guess the extent of revision. The lone Preface was written in 1942. A very few references to literature since the earlier edition are included here and there. References, however, are not cited; they appear only as partially classified lists at the ends of chapters, a feature which sharply restricts the usefulness of the book. Similarly, there is an abundance of good illustrations; but these too are never referred to in the text, and indeed are related hardly at all to it. The legends to figures are inappropriate in a number of cases (e.g., numbers 84, 107, 185, and 186). The new title is a more meaningful one, since the book actually is an account of the ways of insects, emphasizing especially their almost unimaginable diversity. It is, as the author intended, an enjoyable, elementary introduction to all aspects of the lives of our most abundant cohabitants of the earth.

DAVID R. EVANS

BIOGEOGRAPHY AND ECOLOGY IN AUSTRALIA. *Monographiae Biologicae: Vol. VIII.*

Edited by A. Keast, R. L. Crocker, and C. S. Christian. Dr. W. Junk, den Hague. Dutch guilders 65.- iv + 640 pp. + 18 pl.; text ill. 1959.

This volume is a collection of 37 independent articles of great diversity. Most of them fall broadly within the categories indicated in the following list of topics: Physiography and climate of Australia; Survey of natural resources—their utilization by aborigines before 1788 and by Europeans after this date; Surveys of selected groups of plants and animals using taxonomic techniques to infer the origin and history of the Australian flora and fauna; Ecological accounts of the distribution and abundance of particular species or groups of species; and Miscellaneous aspects of the biology of Australian species. This last group is small, but it includes an interesting paper on the physiology of reproduction in marsupials, and another on the adaptations in

physiology and behavior of frogs in relation to the dryness of the places where they can live.

The diversity of subjects is matched by the diversity of their treatment. Some deal with great achievements of the past (the biological control of prickly pear); some discuss the results of current research (the ecology of marsupials, or bird-banding); while others outline experiments so new that they do not yet have any results to report (eco-genetic studies of subterranean clover).

Confronted by such variety, one finds it difficult to generalize; yet there are too many papers to criticize individually. I greatly admired the ecological perspective developed in A. B. Costin's article on the management of water-catchments, in N. C. W. Beadle's account of plant associations in semi-arid regions, in I. M. McDonald's treatment of the merino sheep, and in the account of the ecology of the quokka by A. R. Main, J. W. Shield, and H. Waring. These papers reflect the earthy realism that is characteristic of the best Australian ecology. The spectacular in Australian ecology is represented by A. P. Dodd's account of prickly pear and by F. N. Ratcliffe's story of the rise and fall of myxomatosis.

Notwithstanding the general excellence of most of the individual contributions in this collection, I find myself wondering whether the volume as a whole is likely to achieve its chief purpose. I believe that Australia is an exciting place for a biogeographer, and I know that Australia offers wonderful opportunities for the study of ecology. But I wonder whether the best way to tell the world about this is to throw together in one volume 37 independent and largely unrelated articles. Those articles that contain original material might, in the long run, have made more impact if they had been published in appropriate journals. And if we want to tell the world about Australian zoogeography or ecology, why don't we write proper books on these subjects? A book needs the integrity that comes from being the personal work of one or two authors. This integrity is not likely to be achieved by an editor who merely compiles the writings of a score or more of contributors. I regret the modern custom of publishing scientific miscellanies, masquerading as books, no less for having read this one.

H. G. ANDREWARTHA

GRASSLANDS. *A Symposium presented at the New York Meeting of the American Association for the Advancement of Science, Dec. 27–30, 1956. Publ. No. 53.*

Edited by Howard B. Sprague. American Association for the Advancement of Science, Washington, D. C. $9.00; ($8.00, AAAS Members). xvi + 406 pp.; ill. 1959.

In 1956 the Agricultural Section of the AAAS presented a survey of the role which the grasslands play in our national economy and a review of the knowledge about grasslands. The various papers given are collected in this book. It is the editors' feeling that grasslands have never been given their deserving recognition in production data or in research effort. They are economically important because as a source of directly consumed forage they occupy about twice the cropland areas, and supply about one-half of the feed for our domestic animals. Through grass the nonarable land becomes useful, fertility is maintained, the tillable land is conditioned, soil and water losses are controlled, and worn-out dust bowl areas are reclaimed.

Recognition of the importance of grasslands has improved in the past 25 years, though, for the most part, grass has been taken for granted. Greater improvements are possible through the application of experimental and practical findings, as well as in the management of these grasslands. If such were applied to 1000 million acres supplying 50 to 75% of the cost of producing livestock, the economic importance becomes very apparent. Those concerned with the several aspects of this problem—scientists, engineers, and administrators—should, in the editor's view, welcome such a review as the present one, by specialists on various topics.

The book is a series of short papers, of about 10 pages each, by 44 different authors. These are grouped under the following headings: Science in Support of Grassland Research; Forage Production in the Temperate Humid Regions; Engineering Aspects of Grassland Agriculture; Forage Utilization and Related Animal Nutrition Problems; Evaluation of Nutritive Significance of Forages; Grassland Climatology; Ecology of Grasslands; and Range Management.

The 5 or 6 papers collected under each of these topics give an adequate and interesting panorama of the subject. Some aspects are treated in great detail, while other papers dwell on methods and possible future developments, and even on precise practical applications. These variations are somewhat inherent in the authors and the subjects. In any event, one sees here an enormous job accomplished in a country where most of the forage grasses and legumes are imports, but with a far greater job ahead. The methods and projections are reviewed in this edition so that administrator, engineer, and scientist can each see the other's problem.

Although the book results from the 1956 symposium, it has lasting value in that it is a presentation of methods, as well accomplishments, in a

situation which has many ever-changing variables. It should interest and enlighten those who take the grasslands for granted.

DONALD HEBB

POISON ON THE LAND. *The War on Wildlife, and Some Remedies.*

By J. Wentworth Day. Philosophical Library, New York. $6.00. vii + 246 pp. 1957.

In documenting the damage done by the reckless use of poison sprays, J. Wentworth Day, sportsman and naturalist of the old school, provides us with considerable political and social comment as well. And since he is concerned with the preservation of wildlife, he is not content merely to protest against its destruction, but devotes the latter half of his volume to sage and detailed instructions as to its preservation. I am disposed to think that nature lovers in the United States could profit by his example. Protest is far more effective if pains are taken to furnish ample perspective.

Day's evidence as to the wholesale poisoning of wildlife is convincing enough. For example, the use of a phosphorus compound in spraying Brussels sprouts produced 175 corpses on 46½ acres. Twenty-nine were pheasants and partridge, and 129 various small wild birds. At another site the same treatment left on 28 acres 59 corpses, all but 3 being those of game and small wild birds.

The author is not to be confused with those who inveigh blindly against the use of all "chemicals" in land management, nor to be looked at as an opponent of all technological advance, however great his nostalgia for an older pattern. His plea is for a rational blending of the old and new, utilizing the best of both and respecting values both tangible and intangible. This should be kept in mind by the reader who may be impressed by Day's distaste for some of the methods and consequences of the social revolution in England.

Any revolution, peaceful or otherwise, is quite likely to destroy the good as well as the bad features of the system it overthrows. Thus the Mexican revolution, in dividing up the land, deprived rural Mexico of both capital and management, with the result that for many years Mexico was obliged to import food. The British revolution, inaugurated by Lloyd-George, broke up an ancient system which, whatever its faults, rested on mutual obligation and exhibited a rare example of harmony between man and land. One has only to read Day's tributes to the professional competence and sturdy self-respect of the old generation of gamekeepers to sense that the new order falls short of perfection.

At a time when American experience is showing that large management units are necessary if agriculture is to remain solvent, the break-up of British estates has moved in exactly the opposite direction. In consequence, the small individual owner there is obliged to put his holdings under intensive pressure for immediate cash returns. To this end he, like his American colleagues great and small, finds his model in the techniques of microbiology rather than in the natural landscape. He sterilizes the land in order to produce pure cultures of whatever he grows. Reckless poisoning is one result of this policy.

The replacement of hedgerows, copses, and irregular patches of woodlot with wire fencing and square fields is obviously damaging to the traditional beauty of the countryside. But the cumulative economic effects may be no better. The nurture and harvesting of game has long been an important source of income from the land. Even the rabbit, damaging as he is, could be successfully kept within bounds under the old system and furnished an important source of meat and fur. Hatmakers have gone out of business and an estimated 4s.6d. has been added to the average weekly family food cost since the rabbit has been almost eliminated by myxomatosis.

We are assured that the decline in game production from all causes has, besides reducing land-income from game harvest and the rental of shooting rights, also removed the source of income for a great many whose employment was ancillary to wildlife management and shooting. The harvest itself was a source of sport whose conventions and discipline were rigorous. At the same time, the system that produced abundant game was highly favorable to many other forms of wildlife. Tabulations of stomach contents of birds and other animals are convincing proof that their loss is not to be taken lightly.

It was an Englishman, Sir Francis Younghusband, who said that only two kinds of landscape are satisfying. One, where man had never been; the other, where he had achieved harmony with his environment. The harmony of the traditional British countryside was the result of centuries of trial and error. Its restoration can come only by applying the findings of the laboratory in the light of ecological principles.

PAUL B. SEARS

CONSERVATION. *An American Story of Conflict and Accomplishment.*

By David Cushman Coyle. Rutgers University Press, New Jersey. $5.00. xii + 284 + pp.; ill. 1957.

The academician as well as the layman is provided with a concise review of the American conservation movement in *Conservation*. This easily-read book covers the last half century of the struggles

of conservation leaders, the ensuing politics, and the governmental action. It furnishes the biologist, forester, or social scientist who is teaching a course in conservation with the link between his own discipline and conservation in general. From this standpoint, the book is essential reading for the teacher of conservation. At the same time, it should vitally interest the intelligent citizen and voter who has a decision to make about national conservation issues.

The book is divided into four parts: The Beginnings of Conservation; Reaction, War and "Normalcy"; 1933 and After; and The World. The first three parts are by far the best. In many of the earlier chapters we are made constantly aware of how much of today's conservation achievements are due to the foresight and determination of one man, Gifford Pinchot. Later sections give an excellent account of the conservationists' struggle with various governmental agencies, the Corps of Engineers in particular. If the author had as his purpose to stimulate interest and present the controversial issues in conservation, he has succeeded nobly.

ERICH F. BORDNE

EVOLUTION

SEARCH FOR THE PAST. *An Introduction to Paleontology.*

By James R. Beerbower. Prentice-Hall, Englewood Cliffs. $7.50. xiv + 562 pp.; ill. 1960.

This book emphasizes principles and approaches rather than facts, and as such represents a departure from the form established by the more successful elementary textbooks of paleontology published in recent years. A systematic discussion of the major fossil groups (which makes up the bulk of most texts in this field) is included, but only after a 200-page analysis of the purposes of paleontological research and of the biological and geological bases for any study of fossils. With this background, the systematic part of the book takes on the aspect of an exemplification and elaboration of principles and problems and is thus exceedingly readable and stimulating.

The first, or theoretical, part of the book (Chapters 1–8) is primarily a discussion of the means of deciphering the genetic and ecologic history of fossil populations and of the applicability of these interpretations to broad problems of animal evolution and earth history. In writing this section, Beerbower has injected considerable amounts of pure biology. The biology is extremely well integrated with the paleontology; when an ecologic or genetic principle is presented, for example, it is immediately followed by an evaluation of its usefulness in paleontology. Topics covered include: growth and development, functional adaptation, the genetic system, population genetics, species evolution, the definition and description of species, biogeography, phylogeny, and applications of fossils to stratigraphy.

The final chapters of the book (Chapters 9–21) are devoted to the basic biological and paleontological characteristics of the major invertebrate and vertebrate groups. Plants are not included. In these chapters, a minimum of morphologic terminology and taxonomy is presented, and because of this the volume does not constitute a comprehensive reference source like other books in the field.

The book is well illustrated with charts and original line drawings. Each chapter is accompanied by a list of literature references. The bibliographies are not meant to be comprehensive, but they will be valuable to any student wishing to expand on the salient points of the text.

Beerbower's style is light—bordering in places on the flippant. This approach has been generally successful, however. Although informally written, the book is not always easy to read, primarily because the reader is forced to think. The most significant general attribute of the book is that paleontology is presented as a dynamic field—one beset with problems but one which offers great opportunities for new directions in research.

DAVID M. RAUP

CENOZOIC FORAMINIFERA OF MICRONESIA. *The Geological Society of America, Memoir 66.*

By Shoshiro Hanzawa. The Geological Society of America, New York. $4.50. 163 pp. + 38 pl.; text ill. 1957.

This volume contains the descriptions and records of occurrences of the larger foraminifera collected from Cenozoic formations in the islands of Tinian, Rota, Yap, and Kaisaie. The smaller foraminifera are not described, although the occurrences of pelagic forms are noted. The descriptions are of good quality and are amply illustrated with 38 plates. There are, in addition, 5 useful tables showing the distribution of species in the formations of the area.

Hanzawa had almost completed this monograph before World War II, but unfortunately the outbreak of hostilities resulted in a long delay in publication. Since World War II several papers dealing with the foraminifera of Pacific islands have appeared, and there has been some overlap with the area covered in this study. However, good descriptions and records of occurrences of species never become outdated, and this work is an important reference for any one working in the Indo-Pacific Tertiary.

The monograph contains an interesting discussion of the ages of the formations in Micronesia.

Henzawa recognizes 5 ages, and he assigns to these European stage and series names: Priabonian, Aquitanian, Burdigalian, Pliocene?, and Pleistocene. Some readers, however, may object that these terms, particularly the names of stages, may be misleading, since correlations of the Tertiary between Europe and the Indo-Pacific are still uncertain.

RICHARD CIFELLI

CHAZYAN AND RELATED BRACHIPODS. *Smithson. misc. Coll., Vol. 127, Part 1. Pub. 4253.*

By G. Arthur Cooper. Smithsonian Institution, Washington. $20.00 (2 vols.). xvi + 1024 pp. + 2 folded charts. 1956.

In this comprehensive monograph the author has described and magnificently illustrated the highly diversified brachiopods of the early Middle Ordovician of North America. The work will be invaluable to students of brachiopods, and to geologists concerned with the Ordovician. Evolution of the brachiopods during the Middle Ordovician was rapid; representatives of ten superfamilies first appear here, and the groups already well established are represented by large numbers of genera.

The richest and most varied faunas were collected from the Southern Appalachians, where the author's work with B. N. Cooper has led to the understanding of facies variation, largely by means of paleontologic correlations. The environmental control of the occurrence of many brachiopods is abundantly illustrated. At one place, Pratt Ferry, Alabama, 62 species were found, largely inarticulates known only at this locality.

The majority of the thousand species and 163 genera dealt with in these volumes are new. Such a drastic revision might be unwarranted with less ample collections, but the material amassed for this study was adequate for detailed inspection of the internal features on which the taxonomy is based.

The illustrations are contained in Part 2. The preparations are exquisite, especially the delicate silicified specimens that were obtained by dissolving away matrix limestone with hydrochloric acid. The reader might find the separation of plate explanations from the plates distracting, but this is obviously a concession to keep the price of this enormous work within bounds. Less explicable is the appearance of the illustrations of some species several pages beyond their apparent appropriate places.

Despite its size, this is a remarkably easy work to get around in. The major subdivisions of the brachiopods are grouped according to shell structure. Genera and species can be located by means of annotated alphabetical lists. The stratigraphic section, arranged regionally and alphabetically, contains lists of the brachiopods known from each formation.

ROBERT B. NEWMAN

TREATISE ON INVERTEBRATE PALEONTOLOGY. *Part O Arthropoda 1.*

Edited by Raymond C. Moore. Geological Society of America, New York; University of Kansas Press, Lawrence. $10.50. xx + 560 pp.; ill. 1959.

This book is concerned only with fossil arthropods assigned to the subphyla Onychophora and Trilobitomorpha. The classification within each subphylum and diagnoses of all genera and higher taxa are provided. All but 40 pages of the book are concerned with the class Trilobita. These are devoted to brief discussions and descriptions of unusual arthropods, principally from the Middle Cambrian Burgess shale of British Columbia.

An excellent introductory section to the Trilobita, by H. J. Harrington, provides a modern, detailed, well-illustrated summary of nearly all aspects of trilobite morphology. It is slightly more comprehensive than the fine French summary by P. Hupé in the *Traité de Paléontologie*, Vol. III (Q.R.B., 29: 154. 1954). The only serious omissions are a discussion of evidence concerning cephalic segments in trilobites, and an illustration to show descriptive terms applied to agnostid trilobites. Biologists may be particularly interested in the comprehensive section, by H. B. Whittington, describing and illustrating trilobite development from the minute protaspid to the adult trilobite.

The section on the classification of trilobites prepared by 16 specialists reflects not only the problem of "too many cooks," but also the practical difficulty of trying to classify all known remains of long extinct and often imperfectly understood organisms. Examples of most known genera are illustrated, but the quality of illustration varies from excellent drawings and reconstructions to inaccurate drawings prepared by artists obviously unfamiliar with trilobites, and to generally poor photographs. The quality of the classification within each family also varies from many examples which reflect careful new research to others which are hardly more than uncritical assemblages of superficially similar forms.

The value of this book to the non-specialist is primarily in the introductory summaries to the fossil groups. The specialist will find this book a convenient compilation of information about trilobites, a useful guide to prevailing views on the systematic placement and relationships of known trilobite genera, and a constant companion while preparing new descriptive works.

ALLISON R. PALMER

GENETICS AND CYTOLOGY

CLASSIC PAPERS IN GENETICS.

Edited by James A. Peters. Prentice-Hall, Englewood Cliffs. $3.95 (paper). vi + 282 pp.; ill. 1959.

The editor has gathered together 28 original papers, most of which can be considered to be indeed "classic" papers in genetics. They cover a span of 90 years, from Mendel's classic contribution in 1865 to Seymour Benzer's 1955 paper on the Fine Structure of a Genetic Region in Bacteriophage. Examples of other papers included in this volume are: the final summary and discussion of Über Erblichkeit in Populationen und in reinen Linien (W. Johannsen, 1903; translated by the editor); Sex Limited Inheritance in Drosophila (T. H. Morgan, 1910); Artificial Transmutation of the Genes (H. J. Muller, 1927); Genetic Control of Biochemical Reactions in Neurospora (G. W. Beadle and E. L. Tatum, 1941); and The Gene (L. J. Stadler, 1954).

It is quite obvious that when one attempts to select 28 papers as *the* "classic papers" from thousands published in genetics, one invites criticism of one's choices by other geneticists. For instance, population geneticists may feel slighted that their field is represented by only two papers: Mendelian Proportions in a Mixed Population (G. H. Hardy, 1908); and Unit Character Variation in Rodents (L. C. Dunn, 1921). On the other hand, other geneticists may think that the choice of two papers, The Effects of Unequal Crossing Over at the Bar Locus in Drosophila (A. H. Sturtevant, 1925) and The Bar "Gene" a Duplication (C. B. Bridges, 1936), both about a single locus, is unwarranted. However, before one reedits the volume for James A. Peters, one should consider his reasons for choosing the papers that he did.

The editor states that he has deliberately omitted some papers on microbial genetics to avoid duplicating J. Lederberg's work in editing *Papers in Microbial Genetics* (*Q.R.B.*, 27: 391. 1952). More important, it is apparent that the editor did not intend to compile a complete source book of "classic papers" in genetics for professional geneticists, but rather has attempted to collect a well-integrated group of papers which, to use the words of the editor, "have done much to give form and direction to genetic research" and which can be used in teaching introductory genetics to undergraduates. Each paper is introduced by a short paragraph or two which point out to the introductory student the significance of the paper to the development of genetic concepts. The editor is to be congratulated on these concise remarks, for not only do they give the collection coherence but also without them the book would be of little value to the student.

The publication of this book should be welcomed by all teachers of genetics. It will supply an excellent supplementary text for their courses, and it is well worth the space it will occupy on any biologist's bookshelf as a companion volume to *Great Experiments in Biology*, by M. Gabriel and S. Fogel (*Q.R.B.*, 31: 36. 1956).

THEODORE R. F. WRIGHT

RADIATION, GENES, AND MAN.

By Bruce Wallace and Th. Dobzhansky. Henry Holt and Company, New York. $3.50. xvi + 205 pp.; ill. 1959.

Recent years have witnessed the appearance of many efforts to set forth the issues presented by mankind's increasing exposure to radiation. None has succeeded better than the present attempt. The early portion of the book contains the inevitable discussion of the principles of radiation genetics, concisely and well done. Only one error was detected, where an abnormal hemoglobin is attributed to thalassemia (p. 26). But it is the latter portion of the book which distinguishes it from other similar presentations. Here, in a consideration of the impact of mutation of the genetic structure of populations, is a superb statement at an elementary level of the differing consequences of mutation under the "balance" as contrasted to the "classical" hypothesis. Under either hypothesis, the mutations resulting from an increased exposure to ionizing radiation will ultimately result in defective individuals. But whereas under the classical hypothesis the fitness of the population as a whole suffers in proportion to the increased mutation rate, with a prolonged recovery period, under the balance hypothesis the genetic integrity of the species is not compromised to the same extent, the fitness of the population as a whole suffering much less, with a relatively more rapid recovery from the radiation insult. The authors make clear our present inability to reach judgments concerning the relative importance of balanced versus classical systems in human populations.

Throughout the book the authors avoid, in so far as possible, dealing in eye-arresting figures concerning numbers of defective individuals resulting from radiation. The caution of these two eminent geneticists, much of whose professional careers has been concerned with elucidating the genetic structure of natural populations, makes an interesting contrast to certain other recent efforts to present these matters to the intelligent public.

The concluding section of the book deals with

the complex decisions to be reached in connection with questions of permissible dose, etc., and the urgent need for investigation at many levels. In the very last paragraph we read: "It now seems that man neither can nor need rely on natural selection alone; the genetic effects of radiation are in part responsible for this change. For natural selection man must substitute a conscious direction based on knowledge. The requisite knowledge will soon be forthcoming; let us hope that wisdom lags not too far behind." From his limited knowledge of human genetics, the reviewer can only conclude that the word "soon" was here used in the same temporal context in which the Industrial Revolution would be viewed as a recent event.

Ostensibly directed at the intelligent layman, the book can be read with profit by biologists as well—including geneticists. Indeed, the "intelligent layman" who put his algebra aside many years ago will undoubtedly find some of the concepts involved quite difficult to grasp. This is as it must be. The issues involved are among the most complex with which man has yet grappled, and the process of reaching the necessary decisions is not facilitated by over-simplification or by appeals to to the emotions.

JAMES V. NEEL

TRENDS IN GENETIC ANALYSIS. *Columbia Univ. Biol. Ser., No. XVIII.*

By G. Pontecorvo. Columbia University Press, New York. $4.00. xii + 145 pp. + 1 pl. •1959.

The appearance at this time of a book attempting to discuss recent advances in what might be called the pursuit of the gene is perhaps a mixed blessing. On the one hand, this is an explosive field in which, in the last ten years or so, many exciting discoveries have been made which merit both a comprehensive treatment and a wide audience. On the other hand, progress in this area is still occurring at such a rapid rate that any book on the field is likely to become quickly out of date, in terms of concepts as well as information.

The recombination of chromosome parts is the major tool permitting the geneticist to analyse the organization of the genetic material. Recent advances in this area have largely been achieved through the development of selective techniques, primarily for microorganisms, by which rare individuals of novel genotypes may be isolated with ease from large populations. This makes it feasible to do reliable quantitative studies of rare recombination and mutation events.

The earlier "low resolution" studies had given rise to the notion that chromosome consisted of something like a thread of beads, each bead, a gene, being a genetic unit of function which could mutate but could not be split by recombination. When the physicist increased the resolving power of his tools and entered the atomic nucleus, a whole new world of parts confronted and confused him: so it was with the geneticist upon his entry within the classical gene. In addition to showing new features of the organization of the genetic material, studies of "intragenic recombination" have also revealed that the properties of the recombination mechanism itself appear altered when viewed under conditions of high resolution.

The major portion of this book attempts to review this recent work which bears on the organization of the genetic material and the mechanism of recombination. The first chapter is a discussion of the resolving power of recombination analysis and an attempt to relate this to molecular dimensions. Such a treatment is of necessity rather crude and fanciful. Although it is an impressive thought that the geneticist is dissecting genetic elements at the level of nucleotides within a DNA molecule, this particular point does not merit the twenty pages it gets, especially since much of the discussion is awkward because of the need for information which is not fully treated until later in the book.

The second and third chapters deal with the heart of the matter: the discovery that the genetic unit of function is composed of many parts separable by recombination. This unanticipated complex fine structure has rendered the word gene all but useless and a legion of new terms and old terms in new garb have rushed in to fill the void (nonidentical alleles, site, set, cistron, homoallele, muton, locus, heteroallele, recon).

On the whole, the author's treatment of this material is quite good. His description of the basic methods and essential facts is lucid, although at the interpretive level he tends to be superficial, often introducing ideas from various sources without fully justifying their relevance.

So far, to my mind, the most fruitful concept arising out of this chaos is that of the cistron, a linear portion of the chromosome containing the information required to build a particular protein molecule. Thus mutations which are separable by recombination but affect the same gene product can occur at a variety of positions within a region. However, as Pontecorvo points out, more and more complex functional relationships are being found which are difficult to interpret in terms of a simple cistron. It is thus difficult to ascertain the future usefulness of this notion.

The facts about recombination at high resolution (Chapter 4) are, I feel, not adequately appraised by Pontecorvo. In phage and in *Aspergillus*, the facts suggest that the classical "crossover event" is actually an event in which a cluster of

exchanges occurs within a very small region. This gives unexpected reassortment data when markers are present within this region of clustered exchanges. The data on yeast and *Neurospora*, which are glossed over by the author, suggest, to some workers at least, that the recombination events occurring within genes (gene conversion) are qualitatively different from those which occur between genes (crossing over). Pontecorvo's attitude is that the cases described in *Neurospora* and yeast are aberrant and do not reflect the general situation in these organisms. This I think is avoiding the issue. The results of recombination analyses in yeast, *Neurospora*, *Aspergillus*, and phage are strikingly dissimilar, and these differences must be faced in any general treatment of the problem of the mechanism, or mechanisms, of recombination.

The last topic discussed by Pontecorvo is the non-gametic recombination cycle in fungi. A number of fungi, both sexual and asexual, may go through a process involving the formation of a heterokaryon, then a diploid, in which mitotic crossing over may occur, and finally a return to the haploid condition by means of progressive chromosome loss. The author points out that this system has the principal virtue of a sexual cycle, permitting recombination of chromosomes and chromosome parts, and furthermore, in *Aspergillus nidulans*, which has the usual ascomycete sexual cycle as well, the ancillary mechanism is not much less efficient than the sexual one in producing recombinants. The author mentions, in addition, the variety of bizarre recombination mechanisms available to bacteria, and suggests that the absence of a recombination mechanism in an organism may often reflect a lack of ingenuity on the part of the investigators looking for it rather than its actual absence.

In summary, this book is a personal impression of recent developments principally in fine structure genetics. It is a lucid introduction to an exciting area of genetics. In being subjective, however, it is not a balanced and careful treatment of the material. Still, at least a part of this weakness is certainly due to our lack of knowledge in so recently developed a field, which does not yet permit any clear general notions concerning either gene structure or the mechanism of recombination.

R. S. EDGAR

GENETICS IN PLANT BREEDING. *Brookhaven Symposia in Biology. Number 9.*

Brookhaven National Laboratory, Upton. $1.25 (paper). ix + 236 pp.; ill. 1956.

Any distinction between the applied science of plant breeding and the basic science of genetics is largely one of objective and to a lesser extent of test organism. In certain phases of genetics, fully as much basic information has been accumulated by individuals having applied responsibilities (plant breeders) as by individuals having no such responsibilities (geneticists). This symposium covers a part of the area of mutual interest of these two groups of investigators. The formal sessions may be divided, somewhat arbitrarily, into 4 areas, as follows: (1) uses of changes in the chromosomal complement; (2) character analysis and applications of studies in quantitative inheritance; (3) use of self incompatibility and male sterility; and (4) the use of natural and induced variability.

E. R. Sears presented a scholarly demonstration of the utility of cytogenetic technicques in the solution of a difficult breeding problem. The problem involved transferring selectively a gene for leaf rust resistance from *Aegilops umbellulata* to a common wheat, Chinese Spring. This was accomplished by x-ray-induced chromosome breakage and the subsequent transfer of the desired *Aegilops* chromosome segment to the *Triticum* complement. The use of translocations to "label" and provide a simple means of transfer for otherwise not readily identifiable genes was discussed by E. G. Anderson. The value of such translocations or other chromosomal aberrations in the placing of known genes or the search for new genes was also discussed. The possible utility of induced polyploidy in plant breeding was discussed by G. L. Stebbins. The prime requirements for success appear to be a maximum degree of genetic diversity at the polyploid level in conjunction with what is an almost universal requirement in plant breeding, namely, the facilities to handle large populations under a diversity of environments.

Those aspects of quantitative genetics most useful to the plant breeder are classification and the estimation of parameters which may be useful in the estimation of the type and amount of genetic variability. Classification may be considered as a multiple-sense-impression problem. The usefulness of ideographs and other pictorial representations was discussed by E. Anderson. This approach has been used with considerable success in estimating the importance of introgression as a factor in genetic variability and species development. The estimation of population parameters requires the use of mathematical models. Differing model approaches were presented and discussed by C. C. Cockerham and R. W. Allard. The models presented by Cockerham are the more general. The estimates obtained relate to some broadly defined large population. The approach illustrated by Allard is more specific in that the "population" is comprised of the small group of individuals under test. Each approach may have an area of usefulness. In either case, however, the basic assumptions

underlying the model and the procedures used must be kept clearly in mind if valid inferences are to be drawn.

Self-incompatibility, cytoplasmic sterility, and genic sterility have each been used in plant breeding. The genetic basis for self-incompatibility was reviewed by D. Lewis. This phenomenon can be extremely useful or undesirable to the breeder, depending upon the kind of reproduction involved (sexual or vegetative) and the portion of the plant representing the commercial crop (seeds, leaves, or roots). Sporophytic and gametophytic control of incompatibility are known, and both types are widely distributed throughout the plant kingdom. A considerable fraction of the hybrid corn seed and all of the hybrid sorghum seed are produced through use of the cytoplasmic sterility mechanism. The same mechanism is used in the production of hybrid onions and hybrid sugar beets. The expression of cytoplasmic sterility is dependent upon a cytoplasmic-genotypic-environmental interaction. Where seed is the portion of the crop of primary interest, genetic factors inducing the restoration of pollen fertility are of considerable value. The evidence on the interrelations of cytoplasm and genes was reviewed by D. F. Jones. Cytoplasmic and genic male sterility in vegetable breeding was discussed by W. H. Gabelman.

Genetic variation is a prime requisite for plant breeding progress. This variation may result from natural causes or be induced by various kinds of radiation and by certain chemicals. The importance of naturally occurring variation on a global scale was emphasized by J. R. Harlan. He stressed the need for continued plant exploration and for evaluation and adequate maintenance of such stocks after collection. Results from "composite cross" barley populations were used to illustrate the superiority of certain parental types and the marked continuing improvement obtained over a period of years. One is impressed by the fact that our knowledge of the persistence and methods of utilizing naturally occurring variation is quite inadequate. In view of the inadequacies of our knowledge concerning natural variability, it is difficult to account for the current popularity of studies on radiation-induced variability. Unfortunately, some of the current work has been so poorly conceived and executed as to have limited significance from either a genetic or breeding standpoint. This limitation arises from a failure to control pollination adequately. Many of the presumed mutations can be sufficiently accounted for on the basis of contamination. It is a well-established fact that increased variability follows irradiation, but no one has yet faced the problem of the comparative efficiency of the conventional approach—hybridization or backcrossing accompanied by selection—in comparison with the currently more popular mutation approach. In the latter procedure, even though a desirable mutant is located, the stock must then be freed of chromosomal irregularities before it can have direct commercial value. Mutation breeding may have more utility when natural variability in a species is limited, when one wishes to extend the range of a given species, or when adequate screening techniques can be devised to permit the detection of specific desired mutants. James MacKey reviewed the extensive Swedish and European experience with mutation breeding. The conclusion was reached that the utility of induced mutations had been established; although the final proof, the commercial utilization of new forms, still lies in the future. The possibilities of various types of chemical mutagens deserve attention on the basis of recent results reported for *Drosophila*. The use of induced mutations as an aid in exploring host-parasite relationships was illustrated by G. W. Keitt and D. M. Boone from their work on the apple scab fungus, *Venturia inaequalis*. W. C. Gregory summarized the results from the irradiation of peanuts. Commercial representatives of this species have been thought to be characterized by very limited genetic variability. Following irradiation, a series of agronomically useful types have been isolated. This achievement provides interesting grounds for speculation as to the universality of the destructiveness of x-ray-induced changes. In the absence of detailed information on the nature of the change, however, such speculation does not supply a satisfactory answer. C. F. Konzak described genetic variations observed following high-energy radiation of oats. Response to *Helminthosporium victoriae* and to certain races of *Puccinia coronata* has been thought to be due to members of a single allelic series. A separation of these two responses was achieved.

G. F. Sprague

LES MÉTHODES EN GÉNÉTIQUE GÉNÉRALE ET EN GÉNÉTIQUE HUMAINE.

By Roger Huron and Jacques Ruffié; preface by Albert Vandel. Masson & Cie., Paris. 8,200 fr. (paper). 556 pp.; ill. 1959.

The publication of an introduction to human genetics in the French language is long overdue. This book is addressed to one aspect of human genetics, the statistical methods which form so large a part of nonexperimental studies.

The first part (129 pages) is a brief summary of general principles and is marred by many errors and omissions. The problems that have concerned geneticists for the last twenty years, including fine-structure studies, microbial genetics, position ef-

fects, tetrad analysis, population dynamics, the control of intermediary metabolism, chromosome mechanics, and gene replication, are scarcely mentioned. The language is extraordinarily imprecise. For example, we are told that miscarriages and anomalies are often observed in the offspring of irradiated mothers (p. 13), that dominant lethals produce visible effects in heterozygotes and kill homozygotes (p. 33), and that penetrance is the frequency with which a gene is manifested in the heterozygote (p. 45). We are assured that lower mammals have 24 chromosomes and higher mammals, including man, have 48 (p. 110), and that the compound nature of some salivary bands has been demonstrated by x-ray photographs (p. 115). Many archaic concepts survive in these pages, such as the *Pisum*, *Drosophila*, and *Zea* types of dominance, and the notion that transformation in *Pneumococcus* is a directed mutation. The unconfirmed claims of Benoit and his collaborators to have effected transformations in birds with DNA are accepted without reservation, as is likewise the explanation of equally unconfirmed reports of transformations with grafts and transfusions by Lysenkoists.

The section on methods in human genetics is introduced by a review of common and pathological traits. The Rh system is presented on the Fisher-Race model as a nest of adjacent loci, and it is suggested, without evidence, that two mutations of the D^u type may act as complementary alleles, producing a normal D antigen in heterozygotes. At this stage in human genetics, any attempt to compile an extensive list of simple inherited conditions is bound to be inaccurate, and the present effort is no exception. Leber's disease is considered to be an example of meiotic drive, all of the old claims of partial sex-linkage are accepted uncritically, and sporadic deaf mutism is said to be recessive. Half of the descendants of patients with Huntington's chorea are alleged to be affected.

The last and major part of the book is devoted to statistical methods and their applications to human genetics. Readers who hope for a highly original work like Malecot's *Mathématiques de l'Hérédité*, from the same publisher, will be disappointed. Instead, there is a competent review of probability and statistics as they are applied in human genetics. The mathematics is simple and should be understood by most biologists, yet careful study of this material will give a good foundation in statistical genetics. Maximum likelihood, population genetics, and segregation and linkage analysis are treated in some detail. On the whole, the presentation is comparable to the books of Li and Mather on methods in general genetics. There is an interesting derivation of the coefficient of relationship from matrices of conditional probabilities for 0, 1, or 2 genes in common. Rh gene frequency estimates are developed in an elegant way from partial derivatives and Lagrange multipliers. The discussion of χ^2 emphasizes partition into single degrees of freedom. For the first time in a popular presentation, the unreliability of the Penrose sib-pair method is pointed out.

Despite these praiseworthy innovations, the book suffers from a number of defects, usually on the genetic side. No one familiar with gametogenesis will be concerned by the restriction of gene frequency estimates to large populations of gametes. The Bayes theorem approach to paternity cases based on population genotype frequencies is clearly unsatisfactory, since it leads to choice of the most common blood type among possible fathers. If French courts accepted this peculiar reasoning, it would be a considerable advantage for a French Don Juan to have an uncommon blood type. The appropriate Bayes theorem approach regards all paternal genotypes as equiprobable, and deals only with conditional probabilities. Smith's useful counting methods are omitted, as are recent extensions of maximum likelihood segregation scores. The excellent synopsis of methods of linkage analysis is marred by omission of any discussion of why one method might be preferable to another. As a result, the book should be regarded more as a convenient compilation of the literature, with explanatory notes, than as a definitive and critical selection of the best methods of analysis. There are numerous typographical errors involving proper names ("Holdane," "Stewens," "Morthon," "Suther," etc.), but no mistake was noted in the formulae.

Despite its flaws, this is probably the best book now available on statistical methods in human genetics.

NEWTON E. MORTON

THE CHEMISTRY OF HEREDITY. *A Monograph in American Lectures in Living Chemistry.* *By Stephen Zamenhof. Charles C Thomas, Springfield, Ill.* $4.25. xii + 106 pp.; ill. 1959. Zamenhof presents, in enthusiastic tone, an elementary introduction to some aspects of chemical genetics. He makes the point clearly that his short book is not to be regarded as a complete treatise but merely as a brief account of the present status of a fast-developing research area where few answers are complete or final. This is contrary to the utterly ridiculous claims of the publisher, who states, on the dust jacket: "a comprehensive picture of the complete mechanism of heredity" and "all that is known about the chemical basis of heredity"!

The book is organized in an interesting fashion. Discussion first focuses on the chemical nature of genetic materials, then proceeds to a consideration

of "intermediary systems" (protein synthesis and cell particulates) and thence to "the peripheral reactions" (e.g., enzyme-mediated catalyses). The initial introduction to the chemical nature of the hereditary material is well done in spite of its seemingly awkward placement before a chapter on the chemical structure of nucleic acids. The effectiveness of the following chapter on mutation is hindered by many digressions of purely speculative nature and by misplacements of emphasis. The ensuing chapter on the "intermediary system and cytoplasmic inheritance" is so sketchy as to make it the weakest portion of the book. A good introduction to the concept of genetic blocks is the main theme of the chapter on "peripheral reactions," and a few specific examples of biochemical mutants in man are surveyed in the last chapter. A superfluous digression into a discussion of mutation is unfortunately sandwiched between these two final chapters, to interrupt what otherwise would constitute an excellent sequence of description and thought.

The book assumes exceptionally little background in biochemistry and genetics on the part of the reader, but bacteriophage is discussed with almost no explanatory introduction. The contents are for the most part accurately presented, although there are occasional unqualified statements which are bound to startle the more sophisticated readers (e.g., "everything in the cell is the result of heredity," or the idea that evolutionary oddities, such as the coelacanth, persist through time with little or no change because their rates of mutation are very low). Citations of the original literature and reviews encourage further reading, and an index is provided. The book is not adequate as a useful reference source for the researcher, however, and one wonders if it presents an adequate enough background to the newcomer to the subject, for any real appreciation of most of the papers cited in the bibliography. While there is a very great need for a concise description of genetic principles to use in the education of physicians and medical students, this book definitely does not suffice alone to meet that purpose. It is aimed at that group of physicians and other individuals who want a quick glimpse of a portion of the realm of one of the basic sciences they have not studied for some time or which is far from their current direct line of interest. Such readers will be impressed with the fine mood Zamenhof creates in presenting his subject as a dynamically developing area with an ever-increasing relevance to medical progress.

PHILIP E. HARTMAN

INTERNATIONAL REVIEW OF CYTOLOGY. *Volume VIII.*

Edited by G. H. Bourne and J. F. Danielli. Academic Press, New York and London; The International Society for Cell Biology. $13.00. x + 541 pp.; ill. 1959.

Once again the current volume of this now well-known review series maintains a comprehensive outlook on cytology and cell physiology while at the same time the individual articles are definitive, pertinent, and well-prepared by competent authors. It is impossible to review each article at length and so, except for the listing of titles and authors, it need only be pointed out that few workers in cytology, cell physiology, or molecular biology can afford to ignore its contents.

The articles are as follows: The Structure of Cytoplasm (C. Oberling); Wall Organization in Plant Cells (R. D. Preston); Submicroscopic Morphology of the Synapase (E. de Robertis); The Cell Surface of Paramecium (C. F. Ehret and E. L. Powers); The Mammalian Reticulocyte (L. M. Lowerstein); The Physiology of Chromatophores (M. Fingerman); The Fibrous Components of Connective Tissue with Special Reference to the Elastic Fiber (D. A. Hall); Experimental Heterotopic Ossification (J. B. Bridges); A Survey of Metabolic Studies on Isolated Mammalian Nuclei (D. B. Roodyn); Trace Elements in Cellular Function (B. L. Vallee and F. L. Hoch); Osmotic Properties of Living Cells (D. A. T. Dick); Sodium and Potassium Movements in Nerve, Muscle, and Red Cells (I. M. Glynn); and Pinocytosis (H. Holter).

C. P. SWANSON

ANALYTICAL CYTOLOGY. *Methods for Studying Cellular Form and Function. Second Edition.*

Edited by Robert C. Mellors. McGraw-Hill Book Company, New York, Toronto, and London. $17.50. x + 534 pp.; ill. 1959.

The second edition of this technical treatise has led to a reshuffling of the original order of the chapters, and to the omission of two chapters dealing with x-ray diffraction techniques and with ultraviolet microscopy and microspectroscopy. Of the chapters retained, all but one—that on autoradiography by P. J. Fitzgerald—have been considerably revised, and some are essentially new, even though the list of authors is substantially that of the first edition. This is, therefore, a new book rather than a second edition.

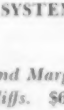
The original chapter on fluorescence microscopy, by O. Richards, has been taken over by Mellors, and is modified into a discussion of the fluorescent antibody method. As such, it deals with a technique of great specificity, comparable in its exactness as an intracellular probe to the Feulgen stain or to highly specific isotope labelling. Its usefulness in tracing immunochemical reactions and localiza-

tions fully warrants its inclusion, and Mellors has presented his topic in a sound and lucid fashion.

The original chapter by A. B. Novikoff, entitled Histochemical and Cytochemical Staining Methods, has been changed to The Intracellular Localization of Chemical Constituents, and is a new treatment. Major emphasis is given to the isolation of subcellular fractions and to specific staining reactions, although other techniques are mentioned briefly where appropriate. R. Barer's chapter on phase, interference, and polarizing microscopy has been revised, but not so extensively; the same holds true for C. C. Selby's article on electron microscopy, and for that by A. W. Pollister and L. Ornstein on the photometric chemical analysis of cells. However, where technical advances have been made, these are incorporated, with the result that in some sections the discussions are either entirely new or have been substantially reoriented. Lastly, the original chapter by A. Engström on historadiography has been altered to x-ray microscopy, with primary attention being given to the use of x-rays for the determination of mass and thickness.

This is obviously a book for the specialist, but even the casual reader will gain the impression that enormous strides have been made in reaching an effective synthesis between morphology and function, both aspects of which are now being viewed at refined levels hardly hinted at a decade ago. It is regrettable, therefore, that the publishers have put such a fancy price on their product; it will keep the book out of general circulation and thus greatly diminish its impact at a time when widespread dissemination of information, particularly among the coming crop of graduate students, is needed to exploit and expand these growing fringes of cytology.

C. P. Swanson



GENERAL AND SYSTEMATIC BOTANY

Plant Life.

By Lorus J. Milne and Margery Milne. Prentice-Hall, Englewood Cliffs. $6.95. xiv + 283 pp.; ill. 1959.

Introductory Plant Science. *Second Edition.*

By Henry T. Northen. The Ronald Press Company, New York. $6.75. xii + 718 pp.; ill. 1958.

Botany. *An Introduction to Plant Science. Second Edition.*

By Wilfred W. Robbins, T. Elliot Weier, and C. Ralph Stocking. John Wiley & Sons, New York; Chapman & Hall, London. $6.95. xii + 578 pp.; ill. 1957.

Botany. *Revised Edition.*

By Carl L. Wilson and Walter E. Loomis; drawings by Hannah T. Croasdale. The Dryden Press, New York. $7.25. xvi + 528 pp.; ill. 1957.

These four textbooks have in common a primary intention to act as an introduction to botany, and they have also in common that none of them is published for the first time, although this is explicitly stated only for the last three. The prices are similar, although their sizes vary considerably, and the variation in amount and quality of the illustrations is also appreciable. The first book has the most pictures and least text and may be intended for colleges at which botany is a minor subject, whereas the other three blend a series of approaches to different phases of botanical science with accounts of phenomena and experiments that are likely to increase the interest of the student in the subject.

The Milnes' book, *Plant Life*, covers different biological phenomena known from lower and higher plants, and its approach is clearly biological rather than specifically botanical. It nowhere delves deeply into the subject. Over 240 pictures and 100 drawings are mixed with the text, which seems to be intended for young students without previous experience in the subject. A rapid perusal of the contents gives the impression that it will prove to be a reliable guide for that purpose.

Northen's book, *Introductory Plant Science*, is intended for more thorough courses in botany. Although it reviews taxonomical, geographical, and genetical approaches, it is essentially physiological, with a slant toward utilitarian points of view. It shows the author to be an experienced teacher, and it is likely to be of great interest to universities with strong inclinations towards agronomy.

The third book, by Robbins, Weier, and Stocking, also serves the needs of agronomy students; it is attractively written and profusely illustrated. All in all, a pleasant and stimulating experience is in store for the student using this book, which is likely to awaken his interest in other approaches to the subject.

The last book, by Wilson and Loomis, is an attractive text intended for students of general botany. It uses so many ways to lure the attention of the reader that one gets the impression that it is aimed at those students who read botany as one of the humanities or for pleasure, rather than for others who are aiming at botany as a profession. It certainly fills the former purpose excellently.

It is common to all four books that their approach is agronomical or physiological and utilitarian rather than taxonomical and evolutionary, although all of them do mention systematics and cytogenetics. The quality of each of them is such as to make it difficult to decide which to select

for a specific course at a particular college or university. Each one is a good addition to the large botanical textbook flora of the New World, although none will really be acceptable as a basic textbook in botany for students who intend to study the subject beyond the introductory level.

ÁSKELL LÖVE

THE PLANT KINGDOM. *A Laboratory Manual. By Paul C. Lemon and Norman H. Russell. The C. V. Mosby Company, St. Louis.* $3.25 (paper). 176 pp. + 19 pl. 1959.

BOTANY LABORATORY MANUAL. *By Erich Steiner, Alfred S. Sussman, and Warren H. Wagner, Jr. The Dryden Press, New York.* $3.40 (paper). 257 pp.; ill. 1957.

PLANT ECOLOGY WORKBOOK. *Laboratory Field and Reference Manual, Revised Edition, 1956. By J. T. Curtis. Burgess Publishing Company, Minneapolis.* $3.25 (paper). iii + 86 pp. + 3 charts; text ill. 1956.

The manual by Lemon and Russell is a typical survey of the plant kingdom, beginning with the lower forms and progressing through the angiosperms. The drawings to be labelled are very well done, pertinent questions are asked of the student to direct his observations and his thinking, and the necessary write-ups are lucid and to the point. That by Steiner, Sussman, and Wagner approaches the plant as a living thing, and weaves structure and function together in a meaningful fashion. Description, except for cells, is left to the last, but as in so many texts and manuals, genetics is hung on as an appendage instead of being treated as one of the central concepts of biology which runs through all of its aspects. One rather good feature of the manual is that the laboratory exercises are cross-referenced to six of the standard botany textbooks, thus enabling the student to find more detailed information quite readily. Curtis' manual deals only with ecology, but in doing so it divides itself into 3 major sections: (1) the laboratory and field exercises which treat of the methods used in ecological studies; (2) reference materials which include various keys for the identification of plants during different seasons of the year, maps of vegetation and soil types, and conversion tables for humidity, vapor pressure, and measurements of circumference and diameter to basal areas; and (3) literature references to the major sources of ecological materials. The manual should prove most adequate for a typical course in ecology.

C. P. SWANSON

EXCURSION FLORA OF THE BRITISH ISLES. *By A. R. Clapham, T. G. Tutin, and E. F. Warburg. Cambridge University Press, New York and London.* $4.50. xxiv + 579 pp. 1959.

An excursion flora is a manual of the plants of a certain area, and is written in such a way that specialists and amateurs alike can use it in order to determine most of the plants they meet in the field. At the same time its size is kept within such limits that the book can easily be carried in a pocket. The essential parts of such a flora are its keys, whereas detailed species descriptions are kept to a minimum, and it is even allowable to exclude the more critical species and most varieties in order to prevent the manual from growing too heavy. Such floras are common in Europe, and they are always well liked by students and casual strollers in the field.

This, the most recent excursion flora I have seen, is based on the authors' splendid *Flora of the British Isles*, which appeared in 1952. The *Excursion Flora* has kept most of the virtues of its more detailed forerunner, and although it is only one-third as thick, it includes almost all of the same species, and even a few that were not in the large manual, because they were then unknown from Britain. Since it is so much smaller than its predecessor, it is handy not only for British botanists doing field work, but also for those foreign visitors who may want to profit from a stroll through the beautiful British countryside by learning its most significant plants without much difficulty.

ÁSKELL LÖVE

FLORA OF THE LAND OF ISRAEL. *By Naomi Feinbrun and Michael Zohary; drawings by Ruth Koppel. Weizmann Science Press, Jerusalem.* $5.00. 15 pp. + 50 pl. 1956.

In two earlier fascicles the authors and artist of this book have published drawings of the plants of Israel. This third fascicle is of the same high quality as were its predecessors, and like the others it includes 50 species typical of the area, from different groups and families. One meets on its pages such old acquaintances as *Agrostis verticillata, Atriplex halimus, Butomus umbellatus, Datura metel, Lythrum salicaria, Oxalis corniculata, Polygonum nodosum, Polypodium vulgare,* and *Urtica urens,* in addition to very many more species not known in northern regions. Notes on the distribution of each species in Israel and also on some of their characteristics are given in the first part of the book, whereas only the Latin and Hebrew names of every species are placed on the plates themselves.

The drawings invariably remind one of the old herbal masters in the technique they employ, although Ruth Koppel has in addition put into them an exactness comparable to that of other modern botanical artists. Although the fascicles hitherto published cover only a small fraction of the re-

markable flora of Israel, they show many of its characteristic plants. The publication is recommended not only to botanical libraries but also to those many lovers of the Holy Land who want to know something about the plants that have covered this area from the remote past.

ÁSKELL LÖVE

ECONOMIC BOTANY

TREE FRUIT PRODUCTION.
By James S. Shoemaker and Benjamin J. E. Teskey. John Wiley & Sons, New York; Chapman & Hall, London. $6.95. viii + 456 pp.; ill. 1959.

The authors have combined their wide experience in practical tree fruit production in Ontario, Ohio, and Florida to produce a well-balanced account of fruit growing of equal value as a textbook or as a source of insight into the principles of orchard management for the commercial grower. A chapter is devoted to each of the major deciduous tree fruits—apples, pears, peaches, cherries, and plums. One chapter considers apricots, nectarines, and quinces, and one the citrus fruits. The importance of dwarfing stocks for apples and pears is recognized in Chapter 3.

The 5 chapters discussing the major deciduous fruits are organized along similar lines. The topics include the areas of commercial production, rootstocks, nursery practice, summarized information on varieties, selection of a site, planting, cultivation, training and pruning, cold damage, fertilizing (including minor elements), pollination, thinning, control of fruit drop, insects, and diseases, harvesting, packaging, and storage.

The authors pay special attention to fertilization and the effect of various nutrients singly and in combination, without neglect of other subjects. The relation of pollination to fruit set in the apple is well covered. The peculiarities of fruit-bud production in the different fruits and their influence on methods of pruning are pointed out. The rather extensive discussion of the training and pruning of peaches is well justified by its importance. The necessity, especially in the southern states, for some provision against sunscald of the scaffold branches when heavy with fruit might have been mentioned. Similarly, warning might well be given against competition between trees and other vegetation such as cover crops or weeds resulting from "trashy cultivation," especially while the orchard is becoming established, in southwestern areas subject to serious dry periods during the summer. The need for sufficient cold to release many of the commercial varieties of peaches from their dormancy is considered.

The dwarfing effects of apple rootstocks developed at the East Malling Research Station in England are presented from tests conducted in the United States. Special requirements for the commercial production of trees on such stocks are discussed. Materials for the chapter summarizing citrus production are well selected.

Throughout the book reasons are given for each operation, and the consequences of various conditions and actions are pointed out. The 103 photographs illustrating the text vary rather widely in quality; many of them are very useful. Outline maps defining the more important areas of commercial production would be helpful. The 803 references to the literature are pertinent. The Index is excellent.

S. H. YARNELL

ADVANCES IN AGRONOMY. *Volumes IX and X. Edited by A. G. Norman. Academic Press, New York; prepared under the Auspices of the American Society of Agronomy.* (IX) $8.00; (X) $12.50. (IX) xii + 308 pp.; ill. 1957. (X) xii + 547 pp.; ill. 1958.

The obvious relationship of the different phases of agriculture to biology is nowhere more apparent than in the annual series *Advances in Agronomy*. This relationship is nicely illustrated in the leading papers of each volume, respectively Agricultural Trends in the Old Cotton Belt, by R. W. Pearson and J. H. Yeager, and Agronomic Trends and Problems in the Great Plains, coordinated by R. V. Olson and written with six other contributors. The first makes clear that, in spite of a 50 per cent increase in acre yield, the importance of the cotton crop to the South declined between 1910 and 1955. Offsetting increased efficiency are government programs, labor shortages, and the ever-present boll weevil. The report on the Great Plains is organized into 7 sections: the area, by R. V. Olson; field crops, by E. G. Heyne; pasture and range crops, by J. R. Harlan; the conservation of soil moisture, by J. C. Hyde; soil fertility, by H. F. Rhoades; irrigation, by H. R. Haise; and wind erosion, by W. S. Chepil. It is significant that native range is now being fertilized and irrigated, weed and brush control are being attacked on a large scale, and marginal lands are receiving attention. Wind erosion can be reduced by compacting, moistening, or roughening the soil, or by protecting it with a cover crop or any type of windbreak. Strip-cropping alone provides insufficient protection.

Four chapters are devoted to plant materials. The one on the lespedezas was coordinated by P. R. Henson, who wrote the first paper on their origin

and history. Of the 140 species described, 15 are native to the southeastern United States and the others to eastern Asia. All but two species are perennial; some are woody. In the paper on culture and utilization, J. D. Baldridge points out that the annual forms lend themselves readily to various systems of rotation. As hay, good lespedeza is comparable with good alfalfa. A rather extensive lespedeza breeding program is described by W. A. Cope. Mechanization has come to the castorbean. The process is based on a short-internode type, which varies in height from 3 to 12 feet. This is a simple recessive to the normal, which may reach 40 feet. L. H. Zimmerman includes an account of the botany, breeding, and production of this important crop in the Southwest. P. F. Knowles presents an unusually complete discussion of safflower in its botanical and agricultural aspects. The chapter New Grasses and Legumes for Soil and Water Conservation, by A. L. Hafenrichter, is organized on the basis of the four major regions of the Country—the Northeast, the Southeast, the Great Plains, and the West. Desirable species and varieties, as well as their cultural requirements and their usefulness in the conservation of water, are discussed for each region. Some attention to the weediness or lack of this characteristic in the plants mentioned might have been appropriate.

Three chapters in Volume IX and one in Volume X deal primarily with soils. The soils of Australia are described in some detail by C. G. Stephens and C. M. Donald, both of Australia. This is followed by a consideration of their deficiencies of major and minor elements. Areas of moderately high rainfall in a sweeping crescent across the northern part of the continent, down a broad belt along the east coast and back toward the west, as well as a much smaller area in the southwest, have given spectacular responses to the application of commercial fertilizers. These are primarily superphosphate and the trace elements copper, zinc, molybdenum, manganese, boron, and iron. The carrying capacity of the range has been increased for some soils to as much as five times the original, through proper management. Braunerde, or Brown Forest soils, are described by R. Tavernier of Belgium and G. D. Smith of the U. S. Soil Conservation Service. Braunerde, or brown earth, as the name implies, encompasses a rather wide range of soil types and has both acid and basic pon-calcareous aspects. The color is based on yellow and red iron hydroxides. The geographic areas involved are central and eastern Europe and the northeastern United States, extending somewhat to the south and mid-west. In his chapter on The Fixation of Phosphorus by Soils, J. B. Hemwall discusses phosphorus compounds in the soil, phosphorus fixation in acid soils and in alkaline and calcareous soils, the fixation of organic phosphorus, and the plant-soil phosphorus relationship. The fourth chapter on soils, by J. A. Vomocil, reviews methods for the measurement of soil bulk density and penetrability. The relation of soil air space to yield of sugar beets is pointed out. Its relation to the well-being of plants in general might be discussed extensively.

Plant nutrition and fertilizers, in their various aspects, constitute the subject of two chapters in Volume IX and of four chapters in Volume X. Of wide appeal should be the chapter entitled Changing Concepts of Plant Nutrient Behavior and Fertilizer Use, by W. L. Nelson and George Stanford. Among the subjects discussed are the use of soil and plant tests, deficiency symptoms, sources of N, P, and K, fertilizer placement, time of application, fertilizer relations with moisture and the lime content of the soil, and liquid versus solid fertilizers. The chapter on Reactions of Ammonia in Soils is well presented by M. M. Mortland. The sorbtion of ammonia by soils may be on colloidal systems, by chemical combination, or both. The reactions of ammonia with clay minerals and with organic matter are discussed at some length. N. T. Coleman, E. J. Kamprath, and S. B. Weed bring the reader up to date on liming practice. Three factors—soil, plant, and liming materials—are considered. The chapter concludes with a discussion of field operations. In a consideration of the role of sulfur in soil fertility, H. V. Jordan and L. E. Ensminger place major emphasis on the uses plants make of sulfur, suitable sources, loss from soils, the sulfur cycle, and results to be expected from the use of sulfur. Wynne Thorn points out with respect to the trace elements that zinc deficiency is the most dramatic. It is seen as chlorosis, rosetting, dieback, and abnormal growth. The control of zinc deficiency is discussed. The Residual Effect of Fertilizer, a subject for optimists, is presented in a common-sense way by R. L. Cook and J. F. Davis. While levels of phosphorus and potassium do build up under good fertilizer practice, changes in fertilizer grade are seldom necessary. In fact, high levels of potassium lead to leaching and intensify magnesium deficiency. Trace elements may accumulate to reach toxic levels. Nutrients that become a part of green manures may be used by succeeding crops.

Corn Plant Population in Relation to Soil Productivity, by G. H. Dungan, A. L. Lang, and J. W. Pendleton, is the sort of article that should be highly popular, if those who already know how to grow corn read it. While pounds of shelled grain per plant are reduced at all levels of fertility as the number of plants per acre increases, the total acre yield increases enormously from 4,000 to 16,000 plants per acre. Rate of planting is dis-

cussed with respect to the four major divisions of the United States. There is an interesting section on changes in plant characters associated with high population rates.

Defoliation and desiccation as an aid to harvest are considered by F. T. Addicott and Ruth S. Lynch. The general morphology and physiology of formation of the abscission layer are described as aids to the understanding of how defoliants operate. Information on the use of defoliants and desiccating agents on various crops is included.

Why race 15B of wheat stem rust is something special, and what is being done about it, are explained by E. C. Stakman and H. A. Rodenhiser. Known since 1939, race 15B suddenly extended its range in the climatically favorable 1950–51 season over most of North America, becoming persistent in the uredial stage in the wheat areas of central and northwestern Mexico. The study of 15B discloses it as a collection of many biotypes. Breeding for resistance is thus highly complicated. It is concluded that "basic researches on the genetics, the physiology, and the ecology of crop plants and of rusts, and of the interactions between them, are required if a permanent solution is attained."

The Contribution of Statistics to Agronomy, by Oscar Kempthorne, points up ways in which statistical analysis can be helpful in agronomic research. Much of the chapter appears to be equally applicable to work with the annual horticultural crops. Background considerations are given major prominence, and mathematical formulas are subordinated.

S. H. YARNELL

BREEDING FIELD CROPS.

By John Milton Poehlman; line drawings by Hannah T. Croasdale. Henry Holt & Company, New York. $8.50. xx + 427 pp.; ill. 1959.

In this volume the photographs, line drawings, and charts are so numerous, are of such excellent quality, and tell their story so well that the reader has a natural tendency to suspect the quality of the text itself. Careful examination discloses the printed matter to be a well-written and carefully selected account of breeding field crops and related subjects. The four objectives, as stated in the Preface, are: (1) to review the principles of plant reproduction and genetics as they relate to breeding, (2) to give an account of the methods and techniques of plant breeding, (3) to relate breeding procedures to the major field crops, and (4) to discuss the more important problems facing the breeder.

The first three chapters, which accomplish the first objective, appear to be addressed primarily to the undergraduate. Chapter 3, Genetics and Plant Breeding, presents a variety of rather complicated subjects, such as quantitative inheritance, polyploidy, and plant breeding, clearly and without over-simplification. A distinction is made between the methods (Chapter 4) and the techniques (Chapter 5) used in plant breeding. The former refers to the bases for selection and crossing with selection in both self- and cross-pollinated crops, and the means of testing selected populations. The latter considers techniques of pollination, field comparisons, testing for disease and insect resistance, and ways to measure quality.

Separate chapters are devoted to the breeding of wheat, oats, barley, rice, flax, tobacco, soybeans, corn, sorghum, cotton, sugar beets, and forage crops. Special attention is paid, where applicable, to origins, species relationships, cytology, genetics, breeding methods, and objectives, and each chapter is concluded with a list of citations, selected references, or both. Such a listing gives no indication of the wealth of detail presented in the discussion of the breeding of each major crop. Attention is called to the special problems of each and the distinctive methods that have been developed as a result of the characteristics peculiar to each crop. A final chapter on seed production practices presents an important subject that might be overlooked by the student. The glossary and index are adequate to the needs of the interested reader. The book should prove to be welcome supplementary reading for the breeder of any crop.

S. H. YARNELL

MANAGING SOUTHERN SOILS.

By H. B. Vanderford. John Wiley & Sons, New York; Chapman & Hall, London. $4.75. viii + 378 pp.; ill. 1957.

The contribution of soil management to crop production in our southern states is discussed in this book. The author emphasizes management principles and gives special attention to fertilizing for crop production, liming, erosion control, and water conservation.

The subject matter is presented in logical sequence, beginning with Soils and Life, the Nature and Properties of Soils, Soils in Southern Agriculture, and Selecting and Managing Soils. Following these introductory chapters comes a discussion of applied aspects such as: Controlling Soil Erosion, Controlling and Conserving Soil Water, Preparing Soils for Crop Production, Liming Sour Soils, and Fertilizing Crops and Soils. The book concludes by relating soil management to field crop production, and considering grassland cropping and special soil uses, land classification and judging, and suggestions for buying farm land. Written especially for agricultural students, farmers, and farm leaders, it is very readable. Illustrations are numerous, and

these have been carefully chosen so that they complement the subject matter.

Anyone dealing with crop production on our southern soils will find this a useful text. Not only will they gain an understanding of wise soil management, but they will also benefit by a better appreciation of southern agriculture. This book deserves to be widely used.

GILBERT H. AHLGREN

GENERAL AND SYSTEMATIC ZOOLOGY

ROTATORIA. *Die Rädertiere Mitteleuropas. Vol. I, Textband; Vol. II, Tafelband.*

By Max Voigt. Gebrüder Borntraeger, Berlin. DM 70.- (Vol. I) 508 pp.; ill. (Vol. II) 115 pl. 1957.

Rotifers remain a fascinating object of study for both amateur and professional microscopists. These two volumes are intended primarily for identification purposes. Following 23 introductory pages explaining characters of taxonomic importance and giving the fundamentals of structure, there are keys to the orders, families, genera, and species found in central Europe. The second volume contains loose-leaf plates illustrating the species. As most rotifers are cosmopolitan, the work should be generally applicable throughout the world, and as such will be welcomed by microscopists everywhere. Unfortunately, the cheap methods of reproduction detract from the work. The text is printed by offset on what looks like mimeograph paper and the figures, similarly done, are small and crowded on the plates. The text descriptions of species are brief, as most emphasis is placed on the figures as means of identification. There are scarcely any bibliographic sources mentioned beyond authors and their dates. The two volumes represent a vast amount of labor that will be appreciated by students of microscopic life.

L. H. HYMAN

A HISTORICAL REVIEW OF THE MOLLUSKS OF LINNAEUS. *Part 7. Certain Species of the Genus Turbo of the Class Gastropoda. Bull. Amer. Mus. nat. Hist., Vol. 118, Art. 5.*

By Henry Dodge. American Museum of Natural History, New York. $1.00 (paper). ix + pp. 211–257. 1959.

To those to whom the success of research is contingent upon the correct identification of the Mollusca named by Linnaeus, the news that the work under consideration is to be the concluding instalment of the series to which it belongs will be a profound disappointment. Failing eyesight has compelled Henry Dodge to leave untouched the Cephalopoda and the remainder of the Gastropoda, among the latter being the rather important genera *Helix*, *Haliotis*, and *Patella*.

This terminal instalment is the briefest that has yet appeared. It treats of only 15 species, only one of which is assigned to the genus *Turbo* today—*T. pethobatus*. This amounts to approximately one-third of the total number of species assigned to this genus by Linnaeus. The identification of some of these is attended with a great deal of difficulty, for reasons adequately explained in the introductory paragraphs. The identification of the remaining thirty-odd species would probably have presented even greater difficulties, for they are scattered about among such divergent families as the Architectonicidae, the Rissoidae, the Cyclophoridae, and the Clausiliidae.

The impairment of one's vision is always a calamity, but especially so when it precludes the completion of one's lifework. Let it be hoped that adequate medical care for the author may enable this treatise to escape the destiny of remaining an "unfinished symphony."

JOSHUA L. BAILY, JR.

A REVIEW OF THE GENUS *BUSYCON* AND ITS ALLIES. *Part 1. Illustrated Contributions to the Paleontology of America. Palaeontographica Americana, Vol. IV, No. 28.*

By S. C. Hollister. Paleontological Research Institution, Ithaca. $4.00 (paper). xii + pp. 59–126 + 18 pl.; text ill. 1958.

ANNUAL REVIEW OF ENTOMOLOGY. *Volume 5.*

Edited by Edward A. Steinhaus and Ray. F. Smith. Annual Reviews, Palo Alto. $7.00. viii + 451 pp.; ill. 1960.

More and more this series contains articles that have a broader, more basic orientation than the word *Entomology* commonly suggests: economic and medical aspects are the concern of only about half of the contributions to the present volume, and the announced topics for Volume 6 contain an even lesser proportion. Volume 5 contains the usual author and subject indices and also cumulative indices to authors and titles of the chapters in Volumes 1 through 5. The contributors and chapter titles in Volume 5 are as follows: Insect Flight Muscles and Their Basic Physiology (E. G. Boettiger); Insect Micromorphology (G. A. Edwards); Neurosecretion in Insects (W. G. Van der Kloot); The Physiology of Excretion in the Insect (R. Craig); Cytogenetics of Insects (S. G. Smith); Chromosomal Variation and Adaptation in Insects

(A. B. da Cunha); The Phylogeny of Coleoptera (R. W. Crowson); Northern Biting Flies (B. Hocking); Evolution and Biology of the Termites (F. M. Weesner); Biology of Fruit Flies (L. D. Christenson and R. H. Foote); Host Selection in Phytophagous Insects (A. J. Thorsteinson); Some Recent Contributions to the Study of the Distribution and Abundance of Insects (H. G. Andrewartha and L. C. Birch); Sampling Insect Populations (R. F. Morris); The Use of Honey Bees in the Production of Crops (F. E. Todd and S. E. McGregor); The Biological Background of Locust Control (D. L. Gunn); Mechanisms of Resistance Against Insecticides (A. W. A. Brown); Some Aspects of the Application of Insecticides (L. R. Jeppson and G. E. Carman); Pesticides in Relation to Public Health (W. J. Hayes, Jr.); and Biological Relationships Between Lice (Anoplura) and Microbial Agents (F. Weyer).

DAVID R. EVANS

ECONOMIC ZOOLOGY

THE PRINCIPLES OF BIOLOGICAL CONTROL.

By Harvey L. Sweetman. Wm. C. Brown Company, Dubuque. $8.75. xii + 560 pp.; ill. 1958.

"Biological control," in the language of the economic zoologist, means the prevention or reduction of the harm caused by injurious animals or plants by using "biological factors," that is, animals and plants that prey upon and destroy the injurious forms. The biological relationships that underlie the method have long been known, not only to naturalists but also to farmers and fruitgrowers. It is said that centuries ago the Chinese peasants made a practice of gathering specimens of the praying mantis for their orchards because they feed on other insects. The effects of the natural enemies of pests would seem, on a casual view, to be of considerable importance, since an immense number of species are predacious and parasitic in habit and feed specifically on the animals destructive to agricultural crops and forest trees. But just how important they are, is, in general, very imperfectly known.

The classic examples of biological control, on which practical operations are still modeled, are those where a plant or animal, transported to another country without its natural enemies, increases and spreads so as to become a devastating pest. On the hypothesis that the natural enemies in the native home, where it is less injurious, are the "controlling factors," these are introduced and occasionally they do in fact reduce the pest to insignificance. Such success is considered to verify the hypothesis, though it is evident that there are large gaps in the demonstration. Furthermore, the catastrophic reduction of the pest population, considered to indicate the importance, in its native home, of its parasites and predators, is not, unfortunately, obtained very often.

In fact, biological control, as a method, is still so very empirical that it is really not possible to reduce it to *principles*, i.e., to reliable generalizations from which the sequence of real events and the conduct of practical operations can be deduced. It is true that some ecologists, after enunciating the question-begging proposition that populations are "regulated," deduce that this is effected by regulatory agencies, which must be biological. This argument, also, is too full of gaps to carry conviction.

We therefore cannot expect a work on the principles of biological control to live up to its title and, in this strict sense, Sweetman's book does not live up to it. On the other hand, if by principles we simply mean a fairly comprehensive collection of facts and theories bearing on the subject, in which workers in the field will find much material useful in their investigations and practical experiments, then we must say that Sweetman's *Principles* is about the only general handbook or compendium of its kind in print at the present time. It will be particularly useful to those working in isolated laboratories and remote from good libraries, and it should be in the hands of all entomologists in that position. Its list of references, though not exhaustive and rather weak with respect to the foreign literature, still constitutes an excellent starting-point for more extensive reading. It contains a great mass of useful information on the biology of both parasites and predators, including microorganisms, and good accounts of some of the more important and successful practical experiments in biological control.

On the theoretical side, and particularly with respect to mathematical theory, which has developed rapidly in various directions during the last forty years, Sweetman's work is inadequate. He does mention a number of the theoretical developments, and the prudent reserve he maintains in regard to them contrasts pleasantly with the intransigent and repetitious dogmatism of some of their supporters. A more detailed analysis would, however, have been desirable. More should have been said also about the possibility of applying genetic principles and techniques to practical problems.

However, in spite of some shortcomings, *Principles of Biological Control* must be rated as a book indispensable to workers in the field and as a comprehensive reference work for everyone interested in the subject.

W. R. THOMPSON

A CRITICAL REVIEW OF THE TECHNIQUES FOR TESTING INSECTICIDES.

By J. R. Busvine. Commonwealth Institute of Entomology, London. 30s. x + 208 pp.; ill. 1957.

With the development of DDT and many other new insecticides over recent years, there has been a considerable increase in the number of insecticide testing techniques. Busvine provides a guide to these techniques—mostly of a laboratory-type. The book should prove both useful and stimulating to biologists and others, including specialists in this field. The twelve chapters include topics on the standardization of insects for tests, stomach poison insecticides, contact poisons, immersion methods, laboratory spray apparatus, repellents, fumigants, residual film tests, as well as apparatus for injection or application of insecticides to individual insects. Discussions are brief, yet usually with sufficient detail to guide the reader. For example, stupefaction methods are reviewed in the chapter on handling insects for tests, and the author cautions on the possible toxic effects of using carbon dioxide. Certain *Drosophila*, bees, and cockroaches have been harmed and possibly other insects may be affected. The use of nitrogen is advised instead. The importance of age, sex, and stage of development, as well as temperature, humidity, and other factors, including group specificity on insecticide efficiency, are also reviewed.

Toxicological statistics are discussed in detail. Busvine remarks that some workers seem to become fascinated by these aspects and make extensive analyses. "As a result, the publication may sometimes intimidate the average biologist instead of encouraging him in a moderate use of statistical analysis." Similarly, some other workers develop such elaborate and costly testing equipment that few other laboratories can or will adopt it. Busvine believes that most workers are far too casual in their choice of test method and the statistical implications of the results. The increasing development of insect resistance to certain insecticides emphasizes the need for using standardized precise methods, yet as simple as possible, to provide basic information on this and other factors. The addition of an index might be helpful to those interested in particular insects or certain factors, but as the author states, the detailed table of contents serves as a guide to the different techniques. A list of 551 references is appended.

HENRY H. RICHARDSON

ANIMAL GROWTH AND DEVELOPMENT

THE CONTROL OF GROWTH AND FORM: *A Study of the Epidermal Cell in an Insect.*

By V. B. Wigglesworth. Cornell University Press, Ithaca. $3.00. x + 140 pp. + 8 pl.; text ill. 1959.

A series of six lectures given in October, 1958, at Cornell University provided the source of the 6 chapters comprising this book. The theme is insect development (post-embryonic) and its control. To a surprising degree the subject is illustrated throughout by a single cell type ("epidermal") of a single insect species (*Rhodnius*). The attempt is successful, partly because that particular cell has been explored so effectively by Wigglesworth and partly because this artificial restriction is abandoned when necessary. The discussion proceeds from a description of the events involved in growth and molting, to the differentiation of hypodermal cells into their several forms, and then to an analysis of mechanisms. By restricting the latter to growth and metamorphosis, the hormonal mechanisms are demonstrated in a direct, integrated fashion; it was possible here to avoid mentioning many disturbing complications by a judicious choice of examples. As befits a book of this type, there is some speculation. Part, naturally, deals with the mechanism of hormone action, a subject for the intrepid. The author suggests that the prothoracic gland hormone is required primarily for protein synthesis (p. 62). In a descriptive sense this is almost surely so, but fundamentally the idea seems unlikely to be any more profitable than the cytochrome notion. Especially startling is the idea (p. 90) that the juvenile hormone activity possessed by extracts of some vertebrate tissues may indicate that those compounds have similar functions in the animal from which they were extracted. A chapter follows that compares the multiple capabilities of insect cells in differentiation with the broader subject of polymorphism, in order to emphasize the generality of multiple, alternative capabilities. A brief theoretical section on integrative factors in growth and differentiation concludes the volume. In general form, the text is best described as an enthusiastic personal narrative of research, though other authors are appropriately quoted and credited. It is authoritative, of course, and cites material that was published as late as the end of 1958. The book obviously is intended for a general audience and can be recommended as such with no hesitation. It is the best introduction to this subject that is now available.

DAVID R. EVANS

ANIMAL MORPHOLOGY

A METHOD OF ANATOMY, *Descriptive and Deductive. Sixth Edition.*

By J. C. Boileau Grant. The Williams and Wilkins Company, Baltimore. $11.00 xvi + 879 pp.; ill. 1958.

Textbooks of human gross anatomy may be grouped into two broad classes, the regional and the systematic, according to the pattern of organization of the descriptive material selected by the author. Grant, by choosing the regional approach, has provided the student with a combined dissecting manual and textbook. The development of the text departs from a strictly descriptive attack on a given region of the human body by offering interpretations and analyses of the several morphological features and relations of the region. The author's rationale is that by interrelating facts the student will be led "inevitably to the apprehending of the underlying principles involved" and "will thus learn to reason anatomically." The text is intended to be "a working instrument designed to make Anatomy rational, interesting and of direct application to the problems of medicine and surgery."

In addition to the inclusion of new material with a clinical orientation, and deletion of much of the material concerned with microscopic structure, the revision has incorporated 34 new illustrations, to provide a total of 862 figures. Many of these are ingenious diagrams, designed to aid the student in comprehending the pattern of a part or region of the body, or a specific relationship within a region. To achieve this objective, the figures are frequently highly schematized, and thus necessitate the use of an atlas in conjunction with the text.

The 1955 version of the international anatomical nomenclature (N.A.P.—Nomina Anatomica Parisiensia) has been adopted, although the older (B.N.A.) terminology is provided in brackets where the newer nomenclature differs substantially. A brief prefatory passage discusses various aspects of nomenclature and the regulations governing it.

Although anatomists may be divided in their opinions of an approach to gross anatomy which deviates from that of the large, standard, systematic textbooks, great numbers of medical students in the past have found Grant's *Method* valuable in understanding human anatomy, and many more are sure to do so in the future.

WILLIAM J. YOUNG

ANIMAL PHYSIOLOGY

LABORATORY EXERCISES IN INVERTEBRATE PHYSIOLOGY, *Revised Edition.*

By John H. Welsh and Ralph I. Smith. Burgess Publishing Company, Minneapolis. $3.50 (paper). viii + 179 pp.; ill. 1960.

The 1949 edition of this manual has been extensively revised and expanded by some 50 pages, chiefly through the addition of many new exercises, while only a few old ones have been omitted. As before, only general directions are given, along with references to appropriate original literature; and the approach is still to survey broadly rather than to study fewer phenomena in greater depth. Much recent material has been added: feeding by *Hydra* (Loomis et al.); trehalose in invertebrates (Fairbairn); the biochemistry of insect mitochondria (Williams et al.); excretion in insects (Ramsay); 5-hydroxytryptamine (Welsh et al.); etc. Recent references and modifications based on these have also been added to many of the exercises retained from the former edition. A welcome change is the incorporation of somewhat more sophisticated experimental methods. This new attitude suggests that student laboratories are becoming better equipped, so as to examine the phenomena more convincingly and more appropriately.

Chromatography is employed several times. The appendices still include the Winkler method (although the much simpler method of Loomis is cited), but also give the preparation of gas mixtures, gas analysis, micro chloride titrations, and the measurement of conductivity. Of the new methods, the electrophysiological ones are the most elaborate. Betty Twarog has written a sensible, brief discussion of recording techniques and problems, and several experiments use these methods. Altogether, the revisions have greatly improved this manual, the only one of its kind.

DAVID R. EVANS

LIGHT, COLOR AND VISION.

By Yves Le Grand. John Wiley & Sons, New York. $11.00 xiii + 512 pp.; ill. 1957.

This is an English translation which is stated to follow closely the original French text except for the inclusion of some recent additions. The aim of the author has been to produce a textbook for opticians, engineers, and architects and to make available to them information and numerical data on the response of the eye to radiation. The text has been divided broadly into two sections. Section A considers such things as the radiant energy sources, photometry, retinal illumination, the trivariance of vision, basic principles of colorimetry, and similar topics. Section B treats such subjects as the anatomy of the eye, photochemistry, electrophysiology, and theories of vision. The author has prepared the text to reflect the viewpoint of a physicist, using mathematical tables and formulae wherever possible. This obsession for giving quantitative subjects Greek letters and deriving their relationships to something else is nonetheless done

with considerable skill and simplicity. Even though the author occasionally admits a derived formula may have no practical significance, the discussions and subject matter are, in general, eloquent and highly readable.

Section B is less extensive than Section A and, as a consequence, less complete. Weaknesses are particularly evident here. You might suppose, for instance, that in the chapter entitled Theories of Color Vision you would learn something about the theory of color vision, but the chapter is really a critique of theories. You will need to read the original sources before the substance of this chapter would have meaning. The author furnishes a selected bibliography for the reader.

HENRY G. WAGNER

PROGRESS IN HEMATOLOGY. *Volume II.*

Edited by Leandro M. Tocantins; 19 contributors. Grune & Stratton, New York and London. $9.75. vi + 290 pp.; ill. 1959.

This, the second volume in a series, brings together an unusually outstanding group of contributors who have reviewed many of the recent significant advances in hematology. For the most part these advances have been made by the contributors themselves and this personal role creates particularly interesting reading.

Contents: Recent, Significant Contributions of Dynamic Cytology to Hematology (Marcel Bessis); Recovery from Radiation Injury, with Special Consideration of the Use of Bone Marrow Transplantation (C. S. Congdon); The Role of Physical Factors in the Sickling Phenomenon (John W. Harris); Humoral Factors in Erythropoiesis (George Brecher and Frederick Stohlman, Jr.); Kernicterus (Richard Day and Lois M. Johnson); Hemolytic Disease of the Newborn due to Fetal-Maternal ABO Incompatability (Patrick L. Mollison and Marie Cutbush); Practical Aspects of the Problem of Blood Preservation for the Purpose of Transfusion (Max M. Strumia); Transmission of Leukemia (Stuart C. Finch); Serotonin: Hematologic Aspects (Marjorie B. Zucker); Chemotherapy of Chronic Myeloid Leukemia, with Special Reference to Myleran (John F. Wilkinson and R. L. Turner); Use of Platelet Transfusions in Hemorrhagic Disease (E. P. Cronkite and D. P. Jackson); Correction of the Hemorrhagic Complications of Esophageal Varices (Charles B. Ripstein); and Lipid Anticoagulants (M. J. Silver, D. L. Turner, and L. M. Tocantins).

This book has an overall orientation toward clinical hematology, although it contains a significant amount of information derived from basic research, much of which has clinical application. These up-to-date and comprehensive reviews, supplied with excellent references, will be of particular interest to all hematologists as well as to biologists working in other fields.

L. K. DIAMOND

BIOCHEMISTRY

BIOCHEMISCHES TASCHENBUCH.

Edited by H. M. Rauen. Springer-Verlag, Berlin, Gottingen, and Heidelberg. DM 69. xvi + 1332 pp.; ill. 1956.

Like all such books, this one has far outgrown the capacity of the ordinary pocket. The amount of varied information compiled and organized between p. 1 and p. 1332 is stupendous; and yet, of course, it will very soon be found insufficient to keep up with the growth of new knowledge of biochemical compounds. After a preliminary chapter on abbreviations and recommended nomenclature, and a brief group of tables of physical units of measurement, tables of correction for temperature and barometric pressure, and tables of conversion for hydrometric readings, temperature scales, etc., there is a long chapter devoted to the physical and chemical properties of biochemical compounds, their compositions, molecular configurations, and characteristics, including optical rotation, absorption spectra, and isotope-containing forms. At p. 581 begins a chapter on stereochemistry and spatial configurations. Succeeding chapters assemble data respectively on Physical Chemistry, Radioactivity, Nutrition, Animal Experimentation, Body and Cell Constituents, Biological Structures (histochemical methods), Biological Functions (hormones, vitamins, enzymes, manometric methods, the toxicology of animal poisons, bacterial toxins, glycosides and alkaloids, antibiotics, mitotic poisons, and microbiological methods), Laboratory Methods (with emphasis on freeze-drying, ion exchange methods, paper chromatography, use of phase systems, centrifugation, precipitation, and filtration), and Statistical Methods. The final chapter, on Laboratory Accidents and First Aid, is followed by an extensive Index.

For all biological and biochemical laboratories, this is an essential reference work.

BENTLEY GLASS

THE STRUCTURE AND FUNCTION OF SUBCELLULAR COMPONENTS. *Biochemical Society Symposia No. 16, held at The Senate House, University of London, on February 23, 1957.*

Edited by E. M. Crook. Cambridge University Press, New York and London. $4.00. viii + 100 pp. + 10 pl.; text ill. 1959.

THE RELATIONSHIP BETWEEN NUCLEUS AND CYTOPLASM. *Proceedings of the Symposium held June 9–11, 1958 at l'Université Libre de Bruxelles, Belgium. Experimental Cell Research, Supplement 6, 1959.*

Edited by J. F. Danielli, J. Brachet, and R. J. C. Harris. Academic Press, New York. $12.00 (cloth); $10.00 (paper). viii + 276 pp.; ill. 1959.

A SYMPOSIUM ON MOLECULAR BIOLOGY.

Edited by Raymond E. Zirkle. The University of Chicago Press, Chicago. $7.50. viii + 348 pp. + 10 pl.; text ill. 1959.

The rapidity with which data are accumulating in the area of subcellular structure and function and the excitement generated by these discoveries have given rise to a number of symposia and symposium volumes within the past several years. The terms "subcellular particles," "ultrastructure," "submicroscopic studies," and "molecular biology" all attempt to convey impressions of the domain of biology being investigated, but no single term stresses the fact that it is a domain where structure and function are no longer separable entities, with one being pursued without regard for the other. Cytology, cell physiology, biochemistry, and genetics are all represented in this endeavor, and no one, fortunately, worries about sharp delineations of fields. The current three volumes belong in this multihybrid category, and may consequently be reviewed together as though bound within a single volume.

The central theme in each volume is the old topic of structure and function, now being viewed by the modern scientist who has electron beams for eyes, microprobes and techniques for analysis, isotopes for scouting forays, and better maps to guide him through the terrain of cellular geography. There is a feeling of expectation and infectious excitement on nearly every page, a feeling that on reaching the next mountain peak a comprehensive survey of all aspects of cellular topography will be afforded, and our ideas will fall into proper place.

The first volume, edited by E. M. Crook, is the least ambitious in its scope, and presents 5 papers given at a one-day session of the Biochemical Society of England. The initial paper by J. D. Robertson is concerned with the ultrastructure of cell membranes and of cell membrane derivatives. He raises the question of whether such structures as the endoplasmic reticulum, mitochondria, and Golgi materials are not actually parts of an interrelated system, alike originating from the plasma membrane by the pinching off of membranous fragments. A similar point of view has been advanced by Kaufmann and Gay, although they view the nuclear membrane as serving as the source for the membranes and ribosomes of the cytoplasm. Are we therefore approaching a stage where the origin of the intracellular cytoskeleton is to be contemplated in a meaningful fashion? It would appear so.

Other papers in the same volume include one by S. J. Holt on the determination of intracellular enzyme distributions by staining methods, a provocative discussion by E. Ernster on mitochondrial structure and its relation to function, one by P. Mitchell on structure and function in the relatively simple cells of bacteria, and a brief report by J. D. Judah and K. R. Rees on changes in cellular components as the result of liver injury.

The second book, *The Relationship between Nucleus and Cytoplasm*, contains 20 papers concerned principally with interactions between nucleus and cytoplasm in so far as these relate to the transfer of genetic information, to the DNA-RNA-protein chain of events, and to the differentiation of both parts of the cell. Organized by the International Society for Cell Biology, the volume should be of great interest to American workers not only for the provocative nature of the articles but also because it represents an excellent cross-section of European cell biology at its productive best. It is quite evident that investigators in Britain, Belgium, France, Germany, and Switzerland have done much to advance this field to the forefront of biological research, and thus to keep alive a great European tradition of fundamental cytological research. Only the article by J. Chayen requires additional comment, if only because it jars one's complacency. In considering the cytochemistry of DNA, Chayen argues that DNA is not necessarily the genic molecule, that it is more likely a messenger of the gene, and that other molecules have an equal right to a similar consideration. His argument is based on the variable amounts of DNA in certain temperature-treated cells, with differences in amount of some 20% remaining to be accounted for. In the face of the evidence of DNA as a transforming substance, and in the light of his somewhat unorthodox cytological methods, Chayen's point of view is difficult to accept, but it is obvious that so fundamental a concept as the chemical nature of the gene must never become so dogmatic as to resist challenge when seemingly contrary evidence turns up. It is unlikely, however, that Chayen's data will upset our current notions.

The volume edited by Raymond Zirkle centers its interest on "molecular" biology, a currently popular term embracing studies concerned with the "analysis of laws which control life on the molecular level." Is it possible that the term is to replace the more conventional one of "biochemistry" which has always seemed rather adequate? Be that as it may, the papers in this volume were presented

at the University of Chicago under the auspices of the Chicago-Frankfurt (Germany) Inter-University Program. The first 10 papers, and 5 of the remaining 12 deal with some aspect of the DNA-RNA-protein triumvirate: synthesis, function, interrelationships, heredity. Other papers treat of enzyme models, mitochondrial structure and function, viral invasions, resistance to infection, electron microscopy, nucleolar function, and mitotic spindles. The list of authors is an impressive one: R. L. Sinsheimer, A. Kornberg, A. Rich, C. B. Anfinsen, M. B. Hoagland, H. Swift, and J. H. Taylor, to mention a few, and the presentations are commensurate with their standing among biologists. The volume is, of course, opportune, as are the other two, and it can only be hoped that the enthusiasm and the discoveries evident on these pages will find their proper place in the whole corpus of biology, and not remain the somewhat isolated and esoteric tail that today seems to wag the biological dog.

C. P. SWANSON

ENZYMES OF POLYNUCLEOTIDE METABOLISM. *Ann. N. Y. Acad. Sci., Vol. 81, Art. 3.*

Edited by Jay S. Roth and 51 other contributors. The New York Academy of Sciences, New York. $5.00 (paper). ii + pp. 513–803; ill. 1959.

The symposium is divided into five parts: Crystalline Pancreatic Ribonuclease; Intracellular Ribonucleases; Polynucleotide Phosphorylases; The Structure and Properties of Synthetic and Other Polynucleotides; and Enzymes of Polydeoxyribonucleotide Metabolism. Each part is further divided into four or five papers which give a remarkably complete picture of the individual topics, in view of the limitations of space. The last four parts together form a compact discussion of polynucleotide metabolism, including the enzymatic synthesis and degradation of ribonucleic acids, the possible localization of these activities within the cell, and an excellent discussion of the physico-chemical properties of the polymers. One cannot help feeling that Part I (Crystalline Pancreatic Ribonuclease) is somewhat out of place in this symposium, since, although there is no question of the importance of this enzyme in ribonucleic acid metabolism, the discussion here is chiefly that of ribonuclease viewed as a protein (i.e. in terms of analyses of amino acid sequence, tertiary structure, immunological behavior, and the relation of structure to function rather than to its role in polynucleotide metabolism. This criticism certainly does not detract from so excellent a collection of papers. Although one year intervened between the symposium and its publication, there have been no major revisions since then of the views presented.

MAURICE BESSMAN

SULPHUR IN PROTEINS. *Proceedings of a Symposium held at Falmouth, Massachusetts, May 1958.*

Edited by Reinhold Benesch, Paul Boyer, W. Robert Middlebrook, et al. Academic Press, New York and London. $14.00. xii + 469 pp.; ill. 1959.

What was apparently the central theme of this symposium, the nature and function of the sulfur atoms in proteins, was met no more than halfway by most of the contributors. This, of course, is a reflection of the very imperfect knowledge of protein structure itself as it relates to function. Thus the measurements about which speculation had to center were frequently no more than the number of disulfide or sulfhydryl groups in the molecule together with some information relating physical state or enzymic activity to the functional integrity of these groups. When it becomes apparent that the analytical methods used for the determination of sulfhydryl groups are far from adequate, the pursuit of inquiry at this level begins to appear futile. That it has not been entirely futile is a tribute more to the ingenuity of the individual participants than to any particular subtlety inherent in the terms of reference of the symposium.

Perhaps the chief value of the published proceedings lies in the definition given to the problems surrounding the chemical study of sulfur-containing proteins. In this respect the volume is unique and to workers in this field indispensable. The opening chapters, and particularly that by J. M. Swan on the chemical modification of thiol and disulfide groups, are especially valuable.

The scope of the symposium was very wide, ranging from the general chemistry of cysteinyl groups in proteins, through serum proteins, metal-containing proteins and enzymes, to muscle proteins. Two final sections deal with virus sulfhydryl groups and cell division. Consideration is restricted, however, to cysteinyl and cystinyl residues, methionine is scarcely mentioned, and apart from its role in cell division, glutathione in biological systems is neglected.

It is apparent that the organizers of the symposium, in attempting to emphasize the chemistry of sulfur-containing groups in protein, fell between two stools. The outlook of many of the contributors is essentially biological, and in neglecting the vexed and difficult question of the SH—S—S dynamic in biological systems, the organizers left themselves without a unifying principle.

The discussion following each paper is reproduced in full, and here it is evident that attempts to broaden the scope either to general questions of protein structure or to general biological phenomena were likely to be curbed. Without doubt this was because of limitation of time, but having regard to the nature of the subject it was unfortunate.

Many of the individual papers are of considerable significance in their particular fields. H. Tuppy's examination of the amino acid sequence about the porphyrin moiety of cytochrome c from several species deserves particular mention, while the sections devoted to cell division and to viruses are noteworthy.

An error in setting up has occurred in the discussion following the paper entitled Disulphide Bonds in Proteins, by J. E. Turner et al. The discussion appearing to conclude on p. 31 actually continues on p. 106.

RICHARD M. SMITH

BIOLOGICAL APPLICATIONS OF INFRARED SPECTROSCOPY. *Ann. N. Y. Acad. Sci., Vol. 69, Art. 1.*

Edited by Robert P. Bauman; 31 other contributors. The New York Academy of Sciences, New York. $3.50 (paper). 253 pp.; ill. 1957.

This volume is a collection of discussions concerning the application of infrared spectroscopy to biological and biochemical problems. The first series of papers is concerned with phenomena of interest to workers in all fields of infrared spectroscopy. The topics covered include fractionation procedures, automatic spectral analysis, intensity measurements, the influence of the molecular environment and hydrogen bonding upon spectra, and the use of aqueous solutions. Not all of the discussions deal directly with biochemical compounds, but the results can be applied to these materials. Many of the papers refer directly to biochemical systems in illustrating the principles under discussion. For example, the use of aqueous media is discussed in connection with solutions of nucleic acids and proteins. The use of heavy water in infrared spectroscopy is also illustrated with these materials. The remainder of the volume is devoted to papers of direct interest to those interested in biological systems. Infrared studies are reported on amino acids, serum and tissue lipides, tissue of all kinds, viruses, and pharmaceutical compounds. A discussion of infrared microspectroscopy ought to be of great interest to all biologists and provides a clear indication of the limitations to be expected with this technique. This paper should also be useful to infrared workers dealing with micro samples. The volume ends with a bibliography of published spectra of various compounds of biological interest. This is restricted to small molecules such as amino acids, lipides, steroids, etc., and makes no reference to macromolecules (proteins, nucleic acids, etc.); it contains references up to 1957. This volume provides a valuable source of information for biologists and biochemists interested in exploring the usefulness of infrared spectroscopy in their own problems. Infrared workers will find it an important addition to their libraries.

LEOPOLD MAY

MICROBIOLOGY

TEXTBOOK OF MICROBIOLOGY. *Seventeenth Edition. By William Burrows; with the collaboration of Richard Janvier Porter and James William Moulder. W. B. Saunders Company, Philadelphia and London.* $14.00. xxiv + 954 pp.; ill. 1959.

"The term microbiology is commonly used in a more narrow sense than its etymology suggests. It does not refer to the broader subject of small or minute living organisms, but rather has come to be restricted to those microorganisms which are directly or closely related to human activity and welfare." Thus Burrows clarifies the apparent discrepancy between the title of his book and the actual subject covered, which I for one believe can be much more unambiguously termed "medical microbiology." Even within this realm the accent is definitely on bacteriology, although the chapters on virology have been expanded and strengthened over previous editions, and rickettsial, fungal, and protozoan parasites also receive attention.

As a text in medical microbiology the value of this volume cannot be denied. One would think it a relatively simple task to revise a textbook already in its 17th edition (the revisions, in more recent years, have occurred at 4- or 5-year intervals). Actually, it is a monumental task, performed effectively by Burrows and his two collaborators, R. J. Porter and J. W. Moulder. The text in many places shows the strain of the assimilation of modern research results into an introductory volume, particularly in the early, more general chapters, but, for the most part, it is clearly written and the pressures of the detailed coverage attempted have engendered surprisingly few outright errors. There are few omissions of importance (among them, antigen conversion). Most of the questionable matters arise from slight ambiguities or from debatable interpretations, as for example where one of the earliest pieces of evidence for an altered enzyme is interpreted as an alternative metabolic pathway (p. 232), or where one reads: "Randomness is the identifying characteristic of spontaneous mutation in that the mutation occurs as a result of the operation of an indefinitely large number of small independent causes rather than one, or at the most a few, large and important causes, i.e. an inducer" (p. 239). It would seem that, if such tremendous detail is desired in a textbook, it might be preferable to expand it slightly into multi-authored volumes similar to the

two Lippincott volumes edited respectively by T. M. Rivers and F. L. Horsfall, Jr., and by R. J. Dubos (*Q.R.B.*, 34: 182. 1959). Under rigorous editorship and by utilizing an array of wisely chosen authors, these two volumes have, in their third (1958) editions, surpassed the Burrows text in clarity and authoritativeness. The other choice, of course, is to eliminate a great deal of minutiae contained in both versions of medical microbiology and to stress the important fundamentals; although such an approach is not in keeping with the general habit of making medical textbooks serve in addition as reference volumes. The Burrows text follows this tradition. It is profusely illustrated with informative photographs, diagrams, and tables, it has a good index, and the text regularly refers to easily accessible footnotes which guide the interested reader to consistently well-chosen recent reviews on each subject under discussion.

PHILIP E. HARTMAN

MICROBIOLOGY. *Second Edition.* *By Louis P. Gebhardt and Dean A. Anderson. The C. V. Mosby Company, St. Louis.* $5.75. 476 pp.; ill. 1959.

This revised textbook designed for an elementary introductory course in microbiology at the college level and is oriented strongly toward bacteriology and those organisms of economic importance to man. It assumes extremely little background in biological subjects or in chemistry and does almost nothing to further the individual's comprehension of microorganisms as cells or as organisms. In fact, numerous dubious comments, superimposed upon a somewhat disjointed and distorted manner of presentation, tend to obscure certain important biological principles. For example, some very poor drawings of representative plant and animal cells (p. 42) are as uninformative as most of the text illustrations. Coupled with these drawings and their obscure labeling is the following comment (on plant cells): "... as we go down the scale in the plant kingdom the structure and nature of the cells and organism as a whole become less complex physically, but more complex chemically, and as we go still further down the scale we are unable to distinguish or actually see the whole organism without the aid of a microscope." Definitions in a brief glossary at the end of the book are equally nebulous and sometimes misleading.

What the book does accomplish fairly well, however, is to enhance the student's appreciation of the importance of microorganisms in man's culture and well-being. The major part of the book is concerned with the topics Sanitary and Industrial Microbiology and The Disease-Producing Microorganisms —Pathogenic Microbiology. The book is totally devoid of instruction in technique. For example, although a procedure for the Gram stain is outlined, for some reason it is presented in nonquantitative fashion so that it can suffice only as a guide to the student in regurgitating the names of dyes at examination time. Similarly, the Szybalski gradient plating technique is presented in a fashion guaranteed to conceal from the student the exact means of performing this ingenious and simple procedure.

The general outline of the course, the general approach to the subject, and the price of the book (which has been maintained in the second edition in spite of an increase in text figures and about 50 additional pages of material) are good for a course oriented as the authors intend. What the book badly needs, however, is a thorough, *critical* third revision of specific items in its present content.

PHILIP E. HARTMAN

ADVANCES IN VIRUS RESEARCH. *Volume VI. Edited by Kenneth M. Smith and Max A. Lauffer. Academic Press, New York and London.* $10.00. viii + 382 pp.; ill. 1959.

The general high quality of reviews in previous volumes is maintained in Volume 6. The first article, by R. L. Steer, includes descriptions first of general procedures and precautions, and then of specific procedures developed for the purification of individual plant viruses. C. A. Porter follows with a listing of the mainly sketchy biochemical changes noted in host plants during virus infections. Problems concerned with the spread of plant viruses are ably discussed in an interesting fashion by L. Broadbent and C. Martini. A new era of studies on bacteriophages, truly bringing these viruses into the realm of physiological genetics, is heralded by S. Brenner in a brief, but solid, review. F. L. Schaffer and C. E. Schwerdt review, in a critical and clear article, the purification procedures for polioviruses and related components, and their physical, chemical, and serological properties. Publications on measles virus are treated by F. L. Black, M. Reissig, and J. L. Melnick. In a fashion that has become his trademark, T. M. Sonneborn has composed the final review, comprising 127 pages of informative reading. This time he centers his attention on the remarkable particles (kappa, pi, mu) found in the cytoplasm of *Paramecium aurelia*, covers data relating to the properties of these particles, and includes an up to date discussion of their possible origins and relationships to other organisms as well as to "normal" cytoplasmic constituents of *Paramecium*.

PHILIP E. HARTMAN

CURRENT VIRUS RESEARCH. *Brit. med. Bull., Vol. 15, No. 3.*

Scientific Editor: C. H. Andrewes. The Medical Department, The British Council, London. $3.25 (paper). Pp. 175–250 + 8 pl.; text ill. 1959.

This special number of the *British Medical Bulletin* contains 15 articles on mammalian viruses. Since progress in this field has depended so strongly on new techniques for isolation, growth, and characterization of the virus particles and infected cells, the first papers in this collection are appropriately devoted to Viral Genetics (Sir Macfarlane Burnet); Tissue Culture (J. C. N. Westwood); and Cytological and Biochemical Techniques (D. A. J. Tyrrell and H. G. Klemperer). Following this we have short papers on the current work on chickenpox, measles, polio, the enteroviruses, influenza, the common cold, the adenoviruses, trachoma, insect-borne viruses, and myxomatosis. All of the papers are very short and, taken together, do give a picture of current mammalian virus research.

In the words of C. H. Andrewes: "The numbers of these new viruses are becoming embarrassing. . . ." The reason it is embarrassing, one is left to suppose, is that the number of different viruses far exceeds the number of different diagnosable diseases. Or is it embarrassing because there is no unifying concept as yet which allows one to make sense of this enormous museum of infectious macromolecules? What is needed and missing from this collection of papers is a summary or a clear statement of an interim hypothesis against which new finds may be tested and old ones reevaluated.

CHARLES A. THOMAS

HEALTH AND DISEASE

IMMUNITY AND VIRUS INFECTION. *Symposium held at Vanderbilt University School of Medicine, May 1–2, 1958. Sponsored by the National Foundation for Infantile Paralysis.*

Edited by Victor A. Najjar. John Wiley & Sons, New York; Chapman & Hall, London. $10.50. x + 262 pp.; ill. 1959.

The bonds which tie the diverse topics of this symposium together are few; its 20 articles vary from short notes on work extensively documented elsewhere to long reviews and speculative discussions. The variety of topics is exemplified by two articles contributed by Sir Macfarlane Burnet, in whose honor the symposium was arranged. His opening address concerns the now-popular subject of theoretical mechanisms of response to antigen stimuli; the second, a review of his contributions and some current thoughts on bacteriophages and the genetics of influenza viruses. Data presented by F. Haurowitz and a note by A. M. Pappenheimer, Jr. mention still more theoretical propositions concerning antibody formation, while the latter also affords a transition from this topic to the problem of immune tolerance, covered in 3 further papers by H. Koprowski, R. D. Owen, and R. E. Billingham. That the allergic state involves the formation of antibodies to pre-existent antigen-antibody complexes is hypothesized by V. A. Najjar and J. P. Robinson, and is lent support by data on high-molecular-weight globulins and their complexes in rhumatoid arthritis presented by E. C. Franklin and associates. This pair of papers represents a significant new theoretical and experimental approach to allergic phenomena. Next, R. J. Wedgwood reviews the properdin complex. Difficulties in defining antibody purification by J. R. McCann and a short note by D. H. Campbell.

The next papers, on viruses, constitute an almost complete departure from the earlier papers. While well-written, these articles share little in common and are so far afield from the foregoing papers that the reasons for their inclusion are questionable, especially since most of the ideas and data covered have been presented in very similar fashion elsewhere. Three final papers, on immunity to poliomyelitis, are in keeping with the general theme of the symposium, acknowledge the sponsorship of the meeting, and call attention to the quantitative data now becoming available from careful attention to research on a problem of practical import. But even here, the authors in large measure depart from immunological discussion to give excessive attention to matters of an epidemiological nature.

Because of the diverse nature of this symposium, portions of the volume will be of interest to research workers in many areas of biology. Its value to the research worker is enhanced by the inclusion of a serviceable index.

PHILIP E. HARTMAN

BIOLOGICAL ASPECTS OF CANCER.

By Julian Huxley. Harcourt, Brace & Company, New York. $3.75. 156 pp. 1958.

Julian Huxley had initially been invited by the late C. P. Rhoads of the Sloan-Kettering Institute for Cancer Research in New York to deliver the first Alfred P. Sloan lecture on the cancer problem. In preparing this lecture, the author became so intrigued with the many ramifications of cancer research that the material covered in the lecture was expanded and published as two separate articles in the *Biological Reviews*. The two articles, to which a considerable amount of new material has been added, form the subject matter of this book.

The book is a short, readable, and interesting review of the biological aspects of the cancer problem. The author emphasizes that cancer is not merely a medical problem, but a fundamental problem in

biology. Nor is cancer a single disease, but an assemblage of many different diseases with common symptoms. The questions pertaining to cancer are interrelated and cut across various disciplines. Basic questions include those in genetics, epigenetics or development, biochemistry, immunology, endocrinology, virology, pathology, public medicine, and human ecology, among other fields.

The book, a survey in which the various biological aspects of the problems in cancer research are presented, is divided into two sections: comparative and genetic aspects of the cancer problem; and viral and epigenetic aspects. There is a comprehensive listing of the comparative distribution of neoplasms in vertebrates, invertebrates, and plants. The book contains a good discussion of tumor genetics, including a discussion of specific and racial differences in the proneness to cancer, and of the relationship of genetic and chromosomal imbalance to the origin of tumors.

A chapter is devoted to carcinogenic viruses and their properties. The Shope papilloma virus of rabbits and that of avian leukosis are compared. The Rous sarcoma of fowl, the Lucké carcinoma of frogs, viruses associated with mouse leukemia, and the milk agent of Bittner are also discussed. Another chapter is devoted to basic biological problems pertaining to viruses, including virus masking, viral replication, bacterial transformation, transduction, etc. The relevance of non-nuclear inheritance in *Paramecium* to the cancer problem is pointed out. Finally, a comparative account is given of tumors and epigenetics with brief discussions of carcinogenesis and therapy. There is a 10-page summary and a good list of references for the serious reader.

ABRAHAM GOLDIN

ADVANCES IN CANCER RESEARCH. *Volume V. Edited by Jesse P. Greenstein and Alexander Haddow. Academic Press, New York.* $10.80. x + 463 pp.; ill. 1958.

This is the fifth volume in an excellent series of reviews. There are 8 review articles in this volume, dealing with various aspects of cancer research. A listing of the titles indicates the broad scope of the research covered.

R. W. Begg writes on Tumor-Host Relations. J. P. Greenstein had stated that "the host-tumor relationship is the key to the cancer problem." This review stresses the effect of the tumor on the host. The presence of the tumor results in systemic effects, including alterations in enzyme activity, metabolism, nutrition, hormone balance, composition of the blood, and structure of tissues.

An important aspect of the host-tumor relation, namely, Anemia in Cancer, is reviewed by Vincent E. Price and Robert E. Greenfield. The origin of anemia in the cancer patient has been the subject of intensive investigation over many years. This subject has been ably reviewed under the heads (a) Incidence of Anemia, (b) Role of Decreased Erythrocyte Formation, and (c) Role of Increased Erythrocyte Destruction. The many pitfalls in methodology and interpretation are pointed out. The advantage of judicious use of radioisotope techniques is emphasized. The authors show clearly how the vast amount of research work on anemia serves to point up the need for additional studies in many areas of ignorance.

Also particularly pertinent to the host-tumor relationship is the article by Waro Nakahara and Fumiko Fukuoka on The Newer Concept of Cancer Toxin. The authors discuss a "toxic substance which is produced by cancer cells and which is responsible for certain systemic changes constantly occurring in cancer bearing hosts." This substance is referred to as "toxohormone" and is stated to decrease liver catalase activity. It is presumably present in all malignant tumors. Although "protein-like in nature," toxohormone has not been completely characterized chemically. The biosynthesis of toxohormone is under study. The authors pose the question as to whether "catalase deficiency and toxohormone production in cancer cells are causally related."

P. N. Campbell reviews Protein Synthesis with Special Reference to Growth Processes Both Normal and Abnormal. The review deals with tumors and rapidly growing tissues. The metabolism of tissue proteins in vivo and protein synthesis in whole cells in vitro are covered. It is pointed out that the amino acid composition of tumor protein and that obtained from normal tissue are strikingly similar. Much progress has been made in the elucidation of protein structure, but to date the synthesis of a specific protein in a cell-free system has not been accomplished.

The Weisburgers, Elizabeth K. and John H., present the Chemistry, Carcinogenicity, and Metabolism of 2-Fluorenamine and Related Compounds. N-2-fluorenylacetamide (2-acteylaminofluorene), intended as an insecticide, was found to cause a variety of neoplasms in rats, so providing a remarkable tool for the study of the genesis of cancer. The subject is reviewed in extenso by the Weisburgers. There is an excellent account of the chemistry of the fluorenamines, including their preparation and properties. Careful structure-activity studies have been made. Carcinogenicity is influenced by the mode of administration and varies with species and strain. Notably, the guinea pig and cotton rat were refractory. A review is presented of the action of the agent on the host and of the host on the agent. The weight of evidence is that the development of cancer is a multi-

stage process. The authors point out that the observations on the induction of neoplasia provide material for further detailed investigation of the stepwise process of carcinogenesis.

A review of Chemically Induced Tumors of Fowls is presented by P. R. Peacock. The problems here are not too dissimilar from those in mammals. Induced tumors in fowl and mammals are similar. Notably, the Rous sarcoma is transmissible by cell-free filtrates, as are other spontaneous fowl sarcomata. However, the author finds that most fowl sarcomata induced by carcinogens are non-transmissible by cell-free extracts. He finds it "reasonable to conclude that cancer is a special type of cell reaction that may be excited by a great variety of factors. . . ."

The data pertaining to Specific Tumor Antigens are reviewed by L. A. Zilber. There is a comprehensive discussion of antigens of filterable and nonfilterable tumors and human tumors. The author presents evidence for the detection of specific tumor antigens obtained with the aid of anaphylaxis following desensitization. Passive anaphylaxis was also used for this purpose. It is suggested that the antigenic structure of tumor cells differs from that of normal cells. It is also suggested that the changes in structure of antigen occurring in malignancy "release the cell from the control of the growth regulating systems of the organism. . . ."

Charles Berman gives a clear account of the extensive data on Primary Carcinoma of the Liver, in discussing incidence, clinical manifestations, morbid anatomy, and etiology. The complex ramifications of this most important problem are made quite evident. Areas for future research are indicated.

The five volumes now comprising the series of *Advances in Cancer Research* stand as a monument to the accomplishments of the late Jesse P. Greenstein, who contributed so much to fundamental cancer research.

ABRAHAM GOLDIN

CANCER. *Nature, Cause and Cure.*
By Alexander Berglas. Institut Pasteur, Paris. Free on request. xx + 154 pp.; ill. 1957.

Berglas is a member of the Cancer Research Foundation of the Pasteur Institute in Paris. The author states that, despite the vast existing literature on cancer, this book was written in the hope of contributing to an early solution of the cancer problem. "This work is submitted in the hope that it may promote international cooperation. . . . It is respectfully dedicated to all men engaged in the fight against cancer." The book is notably endorsed in separate prefaces by Dr. Albert Schweitzer, of Lambaréné-Gabon, French Equatorial Africa; Professor Antoine Lacassagne of the Pasteur Institute, Paris; and Professor Hans Lettré of the Institute for Experimental Cancer Research in Heidelberg.

The book is a provocative attempt at a positive theoretical approach in a most difficult field, in which new and novel ideas are wanting. The arguments can be readily followed by the general reader. The book is divided into two main sections: the Nature and Cause of Cancer, and the Cure of Cancer.

The nature and cause of cancer are certainly, to date, not wholly defined nor well understood. The author reviews the established facts pertaining to cancer, properly emphasizing the ubiquitous nature of potential carcinogenic agents. Areas of controversy are discussed under such headings as the following: (a) cancer develops as the result of mutation; (b) cancer is hereditary; (c) cancer arises because of a delayed development of embryonic cells; (d) cancer is caused by a virus; (e) cancer develops as a result of endocrine disorder; (f) cancer develops as a result of malnutrition; etc. The author contends that cancer is the net result of an attempt of the organism to heal. Cancer is brought on by the action of the chronic noxae which prevent the healing processes in the organism from being completed, which, in turn, leads to a failure of the regulatory mechanism of the organism.

The author's description of the genesis of the cancer cell is generalized. "An injury, or a deficiency in certain substances required for metabolism, leads to defense reactions on the part of the body. De-differentiated cells are produced as in any healing process. If the injury is chronic, then this attempted healing is never concluded.—It is only at the moment when the cells no longer respond to the regulatory mechanism that a preneoplasia becomes a cancer." Attention is focused on the importance of studies of regulatory mechanisms in the adult organism as well as in embryonic development.

In the discussion of the Cure of Cancer, the author reviews the existing treatments, including surgery, radiotherapy, the use of radioactive isotopes, and chemotherapy. The author then discusses "a new approach to the cure of cancer." "My idea is to induce such a high frequency of division on the part of the cancer cell that it will divide itself to 'death,' becoming unviable or losing its drive of rapid division and thus becoming harmless." A mathematical model is presented in the appendix. Certainly, any means by which toxicity for the tumor will be increased relative to toxicity for the host will result in an enhanced antitumor effect. Whether this can be accomplished more readily by the selective inhibition of tumor cells, or by selective stimulation of tumor cells, awaits (as the author indicates) further investigation.

In an epilogue the author makes a laudatory plea for the international cooperation of research workers to "free mankind from this most dangerous disease of our time."

ABRAHAM GOLDIN

PSYCHOLOGY AND ANIMAL BEHAVIOR

THE PRINCIPLES OF PSYCHOLOGY. *Volumes One and Two (Authorized Edition in Two Unabridged Volumes Bound as One).*

By William James. Dover Publications, New York. $5.00 (paper). (Vol. 1) xii + 689 pp.; ill.; (Vol. 2.) vi + 702 pp.; ill. 1959.

Much of modern psychology is based on the work of William James. His thoughts are most clearly explained by him in this book. Dover Publications is to be congratulated for reprinting it in an unabridged edition which is both elegant and inexpensive.

MYRON L. WOLBARSHT

HYPNOSIS AND RELATED STATES. *Psychoanalytic Studies in Regression.*

By Merton M. Gill and Margaret Brenman. International Universities Press, New York. $7.50. xxiv + 405 pp. 1959.

More than a decade has elapsed since the publication by these same authors of a volume, *Hypnotherapy*, which was based mainly on their use of hypnosis in psychoanalytically oriented therapy. During this time both authors have energetically carried on research in the hope of finding answers to such questions as the following: Can susceptibility to hypnosis be determined? Can the hypnosis-inducing process be shortened? Is the hypnotic state physiologically different from the normal state? The research findings were equivocal or negative.

In this volume the authors have concerned themselves mainly with the development of a theory of hypnosis. Using psychoanalytic concepts, they conceive of hypnosis as a state of regression to a primitive level of functioning. No use is made of principles and theories from experimental psychology applicable to an understanding of hypnosis.

To non-psychoanalytically-oriented persons, the value of this book will lie chiefly in the summary of largely negative findings of specific investigations and in the penetrating observations on the factors conducive to hypnosis. These contributions are found chiefly in the introduction and in the first two chapters. Psychoanalysts will welcome the book for its congenial, overall conception of hypnosis.

CLARENCE LEUBA

MEMORY AND HYPNOTIC AGE REGRESSION. *Developmental Aspects of Cognitive Function Explored Through Hypnosis.*

By Robert Reiff and Martin Scheerer. International Universities Press, New York. $5.00. vi + 253 pp. 1959.

When it is suggested to adults in hypnosis that they will regress to a certain childhood age, do they merely act as they imagine they did at the designated age, or do they genuinely feel and function like little children? The authors sought answers to these questions and for that purpose devised numerous, ingenious experiments.

They hypothesized that if, in deep hypnosis, adults were to become completely immersed in the circumstances of a particular childhood age level, such circumstances might reinstate not only memories, but also ways of functioning characteristic of that age. This hypothesis arose out of a thorough, insightful analysis of memory to which the first few chapters are devoted.

The experimental design involved a variety of situations in which previous investigators had shown that children behave differently at different ages. In certain problem situations, the experimenters were interested not so much in whether the regressed subjects could solve the problems, but in whether they used the reasoning processes typical of their designated age level. The hypnotized subjects not only were much more likely to show behavior appropriate for their age level, but they also gave clear indications of fitting genuinely, easily, and without embarrassment into the behavior of childhood. The authors point out that the regressing of adults to childhood may provide a convenient way of studying the development of such important processes as those involved in perception and reasoning.

CLARENCE LEUBA

HUMAN BIOLOGY

THE BIOLOGICAL, SOCIOLOGICAL AND PSYCHOLOGICAL ASPECTS OF AGING.

By Kurt Wolff. Charles C Thomas, Springfield, Ill. $3.75. viii + 95 pp. 1959.

Wolff has attempted, not with complete success, to summarize and synthesize the biological, sociological and psychological aspects of aging. Commendable as such an attempted synthesis is, it falls short of its mark, at least in the biological section, which is hardly biological at all in the sense of dealing with basic regularities and phenomena common to a number of species. Instead, the author recounts in an uncritical manner a number of findings or beliefs about human performance and medicine

which have more or less relevance to the process. The chapter could much more aptly have been called "Some Medical Impressions of Aging" rather than The Biological Aspect.

Fortunately, when the author turns to the sociological and psychological aspects of aging, his familiarity with the practical problem and his insight into some of its origins lead him to a more stimulating and persuasive accounting. Particularly instructive, though probably not novel, is the following passage: "Another factor of great importance for the better understanding of the sociological problems involving old age is our own cultural attitude toward the senior citizen. Our century is the 'century of the child and the youth.' We all are directed toward social and economic goals and are driven by an irresistible force to achieve them. We live in a world of continuous competition and, therefore, we have to work compulsively and strenuously to be able to take a place or to hold one. We live in continuous anxiety and tension for one reason or another. We decide that 'time is money.' We are overburdened with work, have no time for recreation, for relaxation, and sometimes not even for sleep. We lose the connection with Mother Nature and with the rhythm of life. Music, art, literature, for us, are considered a 'waste of time.' We find relaxation not even in our family life, not even in love. Sexuality frequently has taken place of true love, and the responsibilities of our family life make us worry day and night. We live without imagination, without play, without phantasy, without romance. We sometimes lose the feeling of being human beings and do things mechanically and without interest. Then, as the end of our life comes nearer to us, we are exhausted and have the feeling we have not really lived at all. In such a world of tension, of compulsion, of work, and of competition, elderly people are considered a burden. They know it, they feel it, they see and hear it and are unhappy and dejected. Elderly people cannot compete with this modern trend, but they are unable to change it. We, however, can and should do something about it" (p. 46).

Somewhat later there occurs another passage of considerable merit: "... To live generously and unselfishly, to continue to build for a braver future through children, through contributions to the culture, through friendships are ways open for every human being and are I think, the only understandable kind of self-perpetuation after death. Since death is an absolute certainty for everyone, real happiness, personal satisfactions, and contentment depend upon the capabilities of an elderly person to overcome his own clinging to a private, egocentric, separate identity in the interest of other individual's welfare and happiness. *Only he, who gives himself completely without regard for his own person, will at the end be free from anxiety and deep concern, when the last hour is approaching, and remain free and unhampered from emotional crisis in old age*" (p. 76).

By contrast, the quotation from Selye on p. 84 seems to me to be in nearly complete conflict with what most biological students of aging hold tenable: "I would like to end with a few sentences of Selye who wrote: 'True age depends largely on wear and tear, on the speed of self-consumption; for life is essentially a process which gradually spends the given amount of "adaptation energy" which we inherited from our parents. Vitality is like a special kind of bank account, which you can use up by withdrawals but cannot increase by deposits. Each exposure leaves a scar. Since we constantly go through periods of stress and rest during life, just a little deficiency of "adaptation energy" every day adds up—to what we call aging.'"

In summary, this book possesses some value in its latter two-thirds, but is much less useful in the portion dealing with biology—which in this connection appears to be a misnomer.

B. L. STREHLER

BIOMETRY

MATHEMATISCHE STATISTIK. *Die Grundlehren der Mathematischen Wissenschaften, Band LXXXVII. By B. L. van der Waerden. Springer-Verlag, Berlin.* DM 46. ix + 360 pp.; ill. 1957.

This mathematical approach to statistics has grown out of its author's long concern with the practical applications of the subject, prominently in biology. It will demand of its readers a familiarity with calculus, but is not of extreme difficulty. From general considerations of Probabilities and Frequencies, the author proceeds to discuss the Empirical Determination of Distribution Functions, Averages, and Dispersions; Fourier-Integrals and Theorems of Limiting Values; the Gaussian Theory of Errors and Student's Test; the Method of Least Squares; the Estimation of Unknown Constants; the Evaluation of Observed Frequencies; Biological Evaluation; Tests of Hypotheses; Tests of Series; and Correlation. A fourteenth chapter contains 13 tables.

This book will be of value to serious students of biostatistics. It is more theoretical than most comparable books in English, and gives rather fewer practical examples (50 in all). It will be particularly useful to those who need to compare the power of different tests and to select the optimal method for a particular purpose.

STATISTICAL METHODS IN BIOLOGY.

By Norman T. J. Bailey. John Wiley & Sons, New York. $4.50. x + 200 pp.; ill. 1959.

In the jargon of the times, "Dr. Bailey has a good product here." The material of the book is well-organized, sound, and useful. The style is lucid and straightforward and, along with the examples chosen, makes the book enjoyable to read. Bailey is obviously well-informed regarding statistical principles and theory and many aspects of biology. Obviously also, he is a good teacher; the book is written in proper perspective for the many biologists who, although intelligent and technically able in their specialties, are, nevertheless, short on mathematics and statistical "know-how."

Chapter 1 is a fine introduction. Chapters 2 and 3 deal with variability, frequency distributions, estimation, standard errors, and confidence limits. A clear verbal discussion of the concept of significance tests in Chapter 4 is followed in Chapters 5 and 6 by a presentation of tests of significance based on the normal, the t and the F distributions. Chapters 7 and 8 are devoted to the uses of the χ^2 distribution in testing for contingency, goodness-of-fit, and homogeneity.

Simple correlation and regression are taken up in Chapters 9 and 10. In Chapters 11 and 12 the analysis of variance and some experimental designs are considered. Main attention is confined to completely randomized, randomized block, and simple factorial designs. Chapter 13 deals with random samples and random numbers, and gives sound pointers for avoiding bias in the design of experiments, surveys, and censuses. Chapter 14 is devoted to partial correlation and regression.

A good discussion of computing and calculating machines forms the final chapter of the book. This is followed by a short and well-selected list of suggested readings of a more advanced nature and a handy summary of statistical formulae, which is set off by being printed on blue paper. On blue paper also are the appendix tables giving percentage points for the distributions of the standard normal deviate, Student's t, χ^2, the correlation coefficient, and F.

The usual pattern of presentation is to begin a topic with orientative material about the concept involved, to follow with the computational procedures, using interesting examples, and to close with a perspective on the uses, limitations, and generalizations of the procedures and concepts presented, and on the inferences which can be made from statistical results. This is illustrated by the following section titles, each from a different chapter: (i) The general notion of correlation; (ii) Some fallacies in interpreting contingency tables; (iii) The meaning of very small χ^2 values; and (iv) The scope of more advanced designs.

The book is intended to be elementary and of limited scope and raises no general criticism. However, two minor matters may be mentioned. The remarks in the 2-page section of the book devoted to "the scope of more advanced designs" are limited to confounded factorials and fractional replication. Brief reference also might have been made to Latin squares, incomplete blocks, and change-over designs. Furthermore, the remarks about confounding and fractional replication leave the reader at loose ends. With a little more space, simple design patterns illustrating the concepts of confounding and fractional replication could have been given, and reference to particular advanced readings could have been made. For a second matter, the material on avoiding bias in the design of experiments and surveys could have been made even better by developing explicitly the concepts of "experimental unit" and "sampling unit."

Many who are advanced in the use of and the teaching of applied statistics can profit by reading *Statistical Methods in Biology*. It is to be hoped that the author will now produce a more advanced work to include components of variance, covariance analysis, some of the more advanced experimental designs, and possibly the elements of biossay.

H. L. LUCAS

DE OMNIBUS REBUS ET QUIBUSDAM ALIIS

A TREASURY OF SCIENCE. *Fourth Edition. Edited by Harlow Shapley, Samuel Rapport, and Helen Wright. Harper & Brothers, New York.* $6.95. xiv + 776 pp.; ill. 1958.

This excellent collection of scientific classics and commentary well deserves its popularity. First published in 1943, its purpose was to give some realization of how the scientist works, of the body of knowledge that has resulted, and of the excitement of the scientist's search. Written for the person without specialized knowledge, it should be of real interest not only to scientists outside their immediate specialties, but also to prospective scientists, and the faithful but sometimes puzzled relatives and friends of scientists. Nephews are known not to read, but as a gift for that teen-age niece it would be just the thing. The present edition contains new material on advances in several fields, including chapters on Radio Stars (A. C. B. Lovell); The Origin of Life (George Wald); Life in Sputnik (P. Isakov); and Radiations and the Genetic Threat (Warren Weaver).

EVELYN HOWARD

CLASSICS OF MEDICINE AND SURGERY. (*Formerly titled: Epoch-making Contributions to Medicine, Surgery, and the Allied Sciences*).

Collected by C. N. B. Camac. Dover Publications, New York; Henry Schuman, New York. $2.25 (paper). x + 435 pp.; ill. 1959.

ELEMENTARY STATISTICS *with Applications in Medicine and the Biological Sciences.*

By Frederick E. Croxton. Dover Publications, New York. $1.95 (paper). viii + 376 pp.; ill. 1959.

FRUIT KEY AND TWIG KEY *to Trees and Shrubs. Fruit Key to Northeastern Trees. Twig Key to the Deciduous Woody Plants of Eastern North America.*

By William M. Harlow. Dover Publications, New York. $1.25 (paper). x + 56 pp.; ill. 1959.

CULTURE METHODS FOR INVERTEBRATE ANIMALS. *A Compendium prepared cooperatively by American zoologists under the direction of a committee from Section F of the American Association for the Advancement of Science.*

James G. Needham, Chairman. Dover Publications, New York. $2.75 (paper). xxix + 590 pp.; ill. 1959.

AN INTRODUCTION TO THE STUDY OF EXPERIMENTAL MEDICINE.

By Claude Bernard; translated by Henry Copley Green. Dover Publications, New York. $1.50 (paper). xxii + 226 pp. 1959.

EXPERIMENTS AND OBSERVATIONS ON THE GASTRIC JUICE AND THE PHYSIOLOGY OF DIGESTION. *Facsimile of the Original Edition of 1833 together with a Biographical Essay* A PIONEER OF AMERICAN PHYSIOLOGY *by Sir William Osler.*

By William Beaumont. Dover Publications, New York. $1.50 (paper). xl + 280 pp.; ill. 1959.

THE BIOLOGY OF THE AMPHIBIA.

By G. Kingsley Noble. Dover Publications, New York. $2.98 (paper). xviii + 577 pp.; ill. 1959.

FROM MAGIC TO SCIENCE. *Essays on the Scientific Twilight.*

By Charles Singer. Dover Publications, New York. $2.00 (paper). xxxvi + 253 pp. + 14 pl.; text ill. 1958.

While all of these books have been published before, it seems appropriate to recognize their reprinting by Dover Publications. Their quality is typical of the offset work of these publishers; unless weighty or very frequently used, the paperbacks have proven as suitable for me as hardcover editions. The illustrations, of course, often leave much to be desired, though they may suffice. One of these books, that by Harlow, is an exception: it is printed on glossy paper with greatly improved type and photographs. The first four are identical reprints of earlier editions. To the Bernard text I. B. Cohen has added a Foreword. There has been appended to Beaumont's 1833 edition, an address given by Osler in 1902 that concerned Beaumont's work. A brief biography has been added to Noble's volume. The essays of Singer are unaltered except that color plates now appear as halftones and a new autobiographical sketch has been added. Again one must note an irritating habit of this publisher: that of attempting to hide, whenever possible, the date of the volume of which the current one is merely a copy. Since most of the above volumes are classics and all are reprints, further description seems unnecessary.

DAVID R. EVANS

RESEARCH IN THE EFFECTS AND INFLUENCES OF THE NUCLEAR BOMB TEST EXPLOSIONS. *Volumes I and II.*

Compiled by Committee for Compilation of Report on Research in the Effects of Radioactivity. Japan Society for the Promotion of Science, Ueno, Tokyo. $26.50 (2 vols.) (Vol. 1) ii + 823 pp. + 5 pl.; text ill.; (Vol. 2) ii + pp. 824–1824 + 26 pl.; text ill. 1956.

These two large volumes represent an enormous number of scientific studies, conducted by several hundred scientific workers, upon the after-effects of the Bikini nuclear weapons test of 1954, as well as of the Hiroshima and Nagasaki explosions. The section on Meteorology contains 39 articles; Physics, 10; Chemistry, 11; Genetics, 7; Agriculture, 23; Fisheries Science, 49; Economics, 1; and Medical Science, 57. The papers are all in excellent English, and represent an extremely important body of scientific investigation in the field of nuclear weapons effects which up until now appears to have been inexcusably ignored by many workers in the fields concerned.

One of the most unique of such studies, to pick an example, was concerned with the exposure of root tips of the spiderwort, *Tradescantia paludosa*, to radioactive hair (0.000356 microcuries/mg one month after the detonation) taken from one of the Japanese fishermen on the vessel No. 5 Fukuryu Maru exposed to fallout from the blast. The rate of mitosis in the plant was found to be decreased by the exposure to the radioactivity, and chromosome breakage and aberration were significantly increased. Mutations and chromosome aberrations have been observed in wild senna, rice, spiderworts, and veronica plants collected for study in the Nagasaki and Hiroshima areas.

Everyone concerned with the radioactivity of milk, crop plants, and fishes—to say nothing of those studying the pathology of radiation injuries, hematological effects, leukemia, and effects either somatic or behavioral on growing children—will do well to study the appropriate parts of these volumes.

BENTLEY GLASS